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Review Article

ROLE OF STEM CELLS IN CARDIOVASCULAR DISEASES: A LITERATURE REVIEW

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Abstract: *Stem cells are of great significance,, and their development has allowed health care workers to develop new treatment methods with more efficacy. Stem cells possess the ability to divide into all three germ layers but there are many ethical problems related to the use of these cells. Therefore, induced pluripotent stem cells (iPSCs) were developed from the somatic cells, especially fibroblasts to overcome these issues. These cells also have the ability to divide into all three germ layers without any ethical problem. This allows them to advance in the field of stem cells. With their development scientists are now working on developing regenerative medicines. Heart problems are one of the leading causes of death around the globe and these iPSCs can help overcomes these problems with more efficacy and least side effects.*

Introduction

The work in the field of stem cells started in the 19th century and the first ever report of induced pluripotent stem cells (iPSCs) was in 2006. Studies have shown that the cultivation of inner cell masses of murine blastocysts can help in the derivation of embryonic stem cells (ESCs) in 1981 (Evans and Kaufman, 1981). The first ever human embryonic stem cells (ESCs) were obtained in 1998 from the mass of blastocysts of humans (Thomson et al., 1998). There are two major properties and uses of ESCs i.e., pluripotency and self-renewal. A cloned frog was produced in 1958 by injecting the somatic cell nucleus from a xenopus tadpole into an enucleated oocyte (Gurdon et al., 1958). A mammal clone was also produced using the same protocol (Wilmut et al., 1997). New methods and studies showed another one of the most important pieces of information which has led to the discovery of iPSCs. This study showed that every type of cell is regulated by its own master genes which keep the unique identity of cells in the body. This was first proved when a single gene (MyoD) was expressed and it converted the fibroblasts of mice into cells of skeletal muscle (Davis et al., 1987). A set of four transcription factors (Klf4, c-Myc, Sox2, and Oct3/4) was introduced retrovirally into the fibroblasts of mice for the production of mouse iPSCs. These iPSCs were involved in chimera formation as well as in the transmission of germline which allows them to be compared with the ESCs of mice (Hanna et al.,2007). A similar and related set of transmission factors was used for the establishment of human iPSCs (Takahashi et al., 2007). These human iPSCs are also comparable with ESCs of humans just like mice iPSCs. Human iPSCs are not involved in the formation of chimera. Differentiation and maintenance of PSCs (Pluripotent stem cells) is controlled by a homeodomain transcription factor Oct3/4. Expression of Oct3/4 is controlled majorly by Sox2 transcription factor (Masui et al., 2007). Network of pluripotency is mainly controlled by the set of Sox2, Oct3/4 and Nanog transcription factors.

One major proto-oncogene linked with the development of different cancers is c-Myc. This gene allows the widespread activation of transcription and also encodes for proteins involved in the modification of chromatin. Studies have shown that c-Myc can be replaced with L-Myc which is reprogrammed a gene that lacks the ability for

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transformation activity. Sox2 is activated by Klf4 which works as a tumor suppressor or oncoprotein and helps in the release of leukemia inhibitory factor (Niwa et al., 2009). These transgenes were first used in lentiviruses and retroviruses with a risk of developing insertional mutations in the cells. These transgenes are usually silenced when they are reprogrammed into pluripotent cells. They can be activated in some cases without any intention and increase the risk of tumor formation. Nongenetic methods were used later to overcome these problems and other transgenes were developed by the use of the sendai virus, removeable piggy Bac transposons, plasmid vectors and adenoviruses (Okita et al., 2011). The development of iPSCs was a major technological advancement in the field of health and medicine and these cells are capable of gene expression and development as well which are the same as that of ECSs (Embryonic stem cells) and can be developed from somatic cells such as fibroblasts by the help of factors (Takahashi and Yamanaka, 2006). These four transcription factors are also known as "Yamanaka factors" which are named after the scientist who developed them. There has been some major improvement in human iPSCs technology since 2007 and has helped in opening new paths in stem cells field as well as regenerative medicine. This has also helped in the discovery of new drugs and disease modelling as well. These iPSCs have been used for the generation of human disease models since their development and they have also been used for screening of drugs for better efficacy. Some of these advantages are potential to develop novel drugs, avoidance of ethical problems linked with ESCs, ability to produce almost all cell types which are required, better expandability and easier accessibility. There has been some major development in the field of gene editing since the introduction of CRISPR-Cas9 technology. This has allowed scientists to generate specific human iPSCs that are genetically defined depending on the models of disease. These iPSCs technology is one of the major parts of the developing generation and science which can help in development of 3D platforms for cellular incorporation as well as having different types of cells. There has been some major interest in the field of regenerative medicine for the applications of iPSCs. Evaluation of human iPSCs was started in a clinical study conducted in 2014. This study reported the use of human iPSCs which were derived from the RPE (Retinal Pigment Epithelium) cells for the treatment of macular degeneration (Kimbrel and Lanza, 2015).

There is a lack of disease models of human cells and organs to properly understand the pathology of disease, and this has led to less knowledge of the progression of diseases and their related therapies. This challenge can be overcome with the help of in-depth study on stem cells. There has been some major development in the medical and science field by the advancement of technologies in recent years. These advancements have allowed us to find the four transcription factors involved in the synthesis of iPSCs and to obtain these cells from any somatic cells such as fibroblasts. These iPSCs showed greater developmental potential and a well-defined profile of gene expression (Takahashi and Yamanaka, 2006). There are various secondary factors including: SV40 large Tag (Simian Vacuolating Virus 40 large T antigen, Lin28, and NANOG which have also been used for genetic modification as they have greater efficacy for developing iPSCs from somatic cells (Spence et al., 2011). The ESCs (embryonic stem cells) and iPSCs (induced pluripotent stem cells) represent relative properties such as ability to develop into each germ layers (endoderm, mesoderm and ectoderm) as well as ability to re-new unlimited times. Studies have shown that iPSCs are more reliable to use with the least risk factor of rejection as compared with ESCs. This process of obtaining iPSCs from somatic cells is usually a very long and time taking procedure. This is why the use of iPSCs in morbidities like injuries and acute disorders is quite limited due to their development process (Kimbrel and Lanza, 2015; Scudellari, 2016). Human, iPSCs were first clinically investigated in 2014 by Riken Institute in Japan. Region specific and tissue specific cells lines can be obtained by the proper use of cytokines, patterning factors, inhibitors and specific growth factors in proper concentration, order and combination when iPSCs are prepared. This technology has allowed medical workers and scientist to understand and study the molecular mechanisms of disease in various cells, development of regenerative drugs, and screening of drugs as well (Sinha et al., 2015) .(Fig. 1). The effectiveness of treatment is still limited in major heart diseases despite great progress in understanding the pathophysiology and cardiovascular disorders as well as great improvement in surgical and medical methods for these cardiovascular diseases. Most of the treatment methods focus on dealing with the progression of diseases or curing the symptoms. One of the major challenges in therapeutics is the repairing of the myocardium which is damaged following the

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infraction. Clinical trials and studies have showed that cell-based therapy is quite promising in repairing the damaged myocardium (Laflamme et al., 2007). ESCs (embryonic stem cells) and adult cells have shown promising results in the treatment of ischemic heart disease (Tongers et al.,2011). Recent studies have shown that this process of autophagy mostly works for the survival of cellular pathway. This pathway is important for the immunity and development in human physiology. This pathway is important for immunity and development in human physiology.

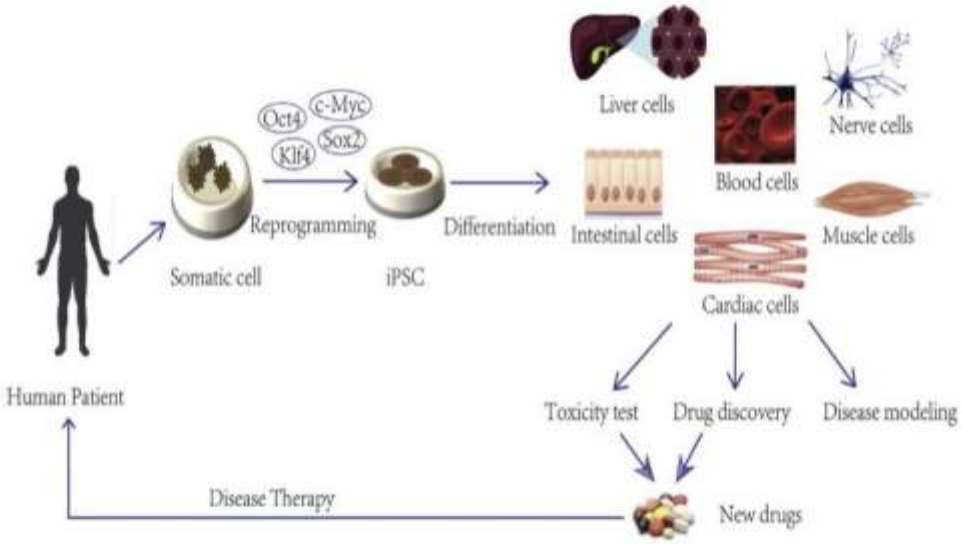

FIGURE 1: USES OF IPSCS IN MEDICAL THERAPY, DISEASE MODELLING AND DRUG DELIVERY

Problems in this pathway can cause numerous disorders such as neurodegenerative disorders). Studies have revealed that autophagy is one of the most important pathways for quality control for the proper functioning of adult and embryonic stem cells which is a role of homeostasis of autophagy (Galluzziet al., 2018; Naidoo et al., 2017). Autophagy is started by the genesis of a phagophore in mammalian cells.

This phagophore is an isolation membrane structure which is obtained from the ER (endoplasmic reticulum) domains known as omega some and can also be obtained from other sources such as mitochondria, plasma membrane, trans-golgi and recycling endosomes (Mercer, 2018). This phagophore later expands and engulfs the autophagic waste of cell which is composed of some macromolecules such as damaged organelles (mitochondria) or other aggregates of protein. This dynamic turnover of autophagosomes (autophagosome flux) and autophagic cargo (autophagic cargo flux) is collectively referred to as autophagic flux waste is covered by a double membrane structure which is known as autophagosome. Autolysosome is formed by the fusion of lysosome with this waste filled autophagosome. Then this waste stored in autophagosome is degraded by the help of lysosomal digestive enzymes in the lysosome (Li et al., 2014). Maturation of autophagosome is mostly completed in multiple steps. This autophagosome mostly fuses with organelle which is known as amphisome. This hybrid organelle acts as a sink for the autophagic bodies in the autophagosome and helps to deliver this waste to lysosome. The autophagosome can also directly fuse with lysosome as well and does not need this process of amphisome formation (Jiang et al., 2019) .(Fig. 2). In the next section we are going to discuss the potential of induced pluripotent stem cell in regeneration of cardiac myocytes and also the neuroglial damage

APPLICATIONS OF IPSCS IN CARDIOVASCULAR DISORDERS

There has been a rise in the mortality rate due to cardiovascular disorders even with the new advancements in the field of medicine (Sidney et al., 2016). Adult cardiac cells do not have much proliferation ability which makes them insufficient to heal any damage or loss of cardiomyocytes in the cardiac area. The chances of scar formation due to

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damage to cardiomyocytes is very high in healing process. Therapies based on medicines do not have the ability to repair the injury or restore the cells in that area after myocardial infarction. There has been major development in the use of adult stem cells in therapeutics since their discovery. These approaches have been using mesenchymal stem cells or progenitor stem cells in therapeutics for repairing the injury. There are reports which have shown the use of many progenitor or stem cells for the treatment of functional and structural abnormalities in the field of cardiovascular medicine (Carvalho and Giaretta, 2013), and it has been reported that scar formation, inflammation and fibrosis was reduced by the use of stem cell therapy which also helped in the recovery of the myocardium as well (Fernandes et al.,2015).

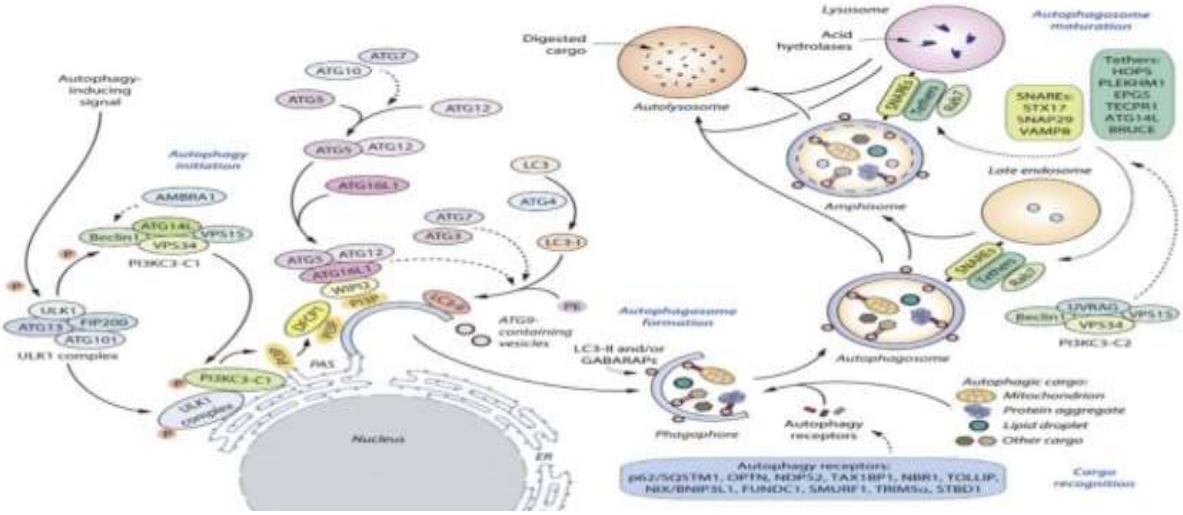

FIGURE 2: MECHANISM OF AUTOPHAGY PROCESS

There has been great deal of study conducted in the use of human iPSCs, smooth muscle lineages, and endothelial cells for their use in cardiovascular problems. iPSCs which were derived from the fibroblast were used in mouse models and they showed promising results in repairing the heart damage and helped in the regeneration of endothelial tissues, smooth muscle, and cardiac muscles as well. These iPSCs were able to engraft in the heart area without causing any damage to cyto-architecture and they also helped in improving the electrical stability, ventricular wall thickness, and contractile performance as well. There are studies which showed that the tumorigenesis is induced in the heart by the intramyocardial injection of undifferentiated iPSCs (Zhang et al., 2011). These results have made scientist wary about the use of stem cells and also forced them to work on differentiation of iPSCs into specific types for a safe transplantation of cells.

Recent studies showed the development of human iPSCs from adult human skin fibroblasts and human umbilical vein endothelial cells using a containing Oct4, Sox2, Klf4, cMyc and Lin28 with lipofectamine as a transfecting agent. These iPSCs were further differentiated into functional cardiomyocytes that have therapeutic potential (Thangavel et al., 2015). combination of plasmid DNA containing Oct4, Nanog, Sox2 and Lin28 and a cocktail of mRNAs

MODELLING OF CARDIOVASCULAR DISEASE AND IPSCS BASED CLINICAL THERAPY

There is a massive role of iPSCs in modelling cardiovascular disorders, gene therapy and cardiotoxicity drug/screening discovery (Jarvis et al.,2014). (Fig. 3). iPSCs which have been derived from patient cardiomyocytes can help in stimulation of human condition as a better option These iPSCs can also be useful in the understanding of cellular signalling pathways, validation of drugs test and molecular physiology This technology of iPSC can also help in understanding the pathobiology of disorders such as catecholaminergic polymorphic ventricular tachycardia and long QT syndrome as well(Chow et al., 2013).

ROLE OF IPSCS IN LEOPARD SYNDROME:

LEOPARD syndrome is an autosomal disorder of envelopment. It is basically Noonan syndrome with multiple lentigines (NSML). There is a

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mutation n the PTPN11 gene which is a missense mutation in most cases of NSML and this gene is involved in encoding of protein tyrosine phosphatase protein (SHP2). One of the major phenotypes is hypertrophic cardiomyopathy in most NSML patients. One of the studies revealed that cardiomyocytes based iPSCs obtained from NSML are larger in size and the nuclear factor of activated T cells.

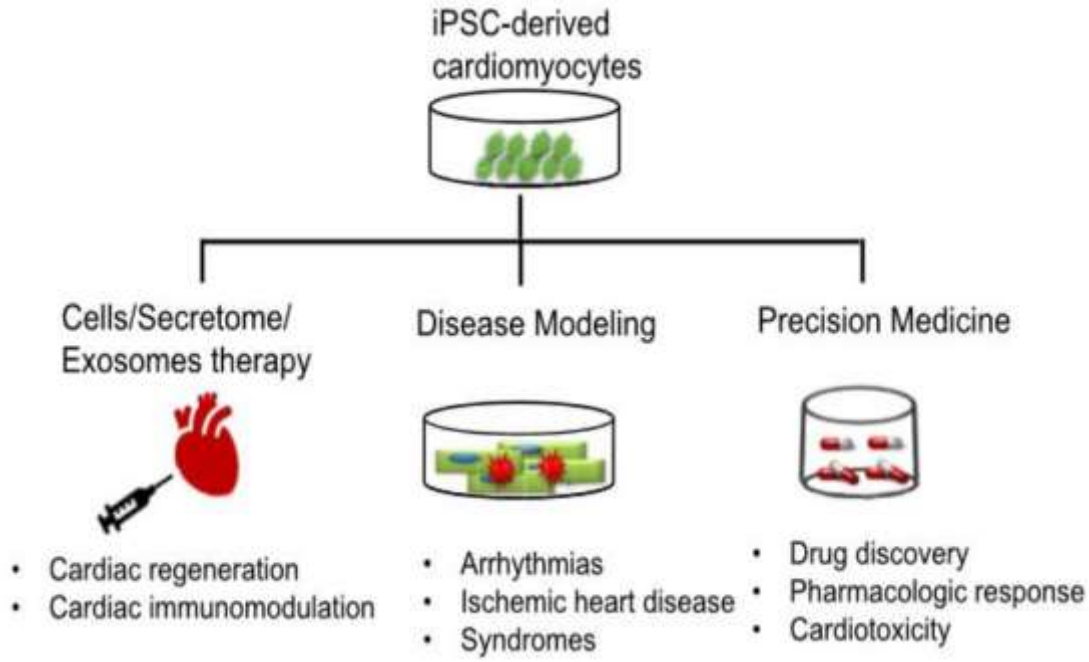

FIGURE 3: POTENTIAL USE OF IPSCS-DERIVED CARDIOMYOCYTES

ROLE OF IPSCS IN LONG-QT SYNDROME:

LQT is an inheritable syndrome. Long-QT has 3 types. In Long-QT syndrome there is an abnormal ventricular phase of "change in membrane potential" which is prolonged and can cause ventricular tachycardia and sudden cardiac death. This disease was studied by obtaining human iPSCs from long-QT syndrome patients (Vanham et al., 2019). One of the studies showed the generation of iPSCs with the help of primary fibroblasts obtained from type-1 long-QT syndrome patients and these iPSCs were able to differentiate into cardiomyocytes respectively. These cardiomyocytes derived from iPSCs showed a prolonged action potential and altered potassium channel delayed current (IKs) as well. Later studies showed that these patient-based cells had an abnormal response towards stimulation of catecholamine stimulation and there was a protective effect on cardiomyocytes derived from iPSCs also observed with beta blocker treatment.

CARDIOMYOPATHY

Progressive heart failure, systolic dysfunction and ventricular dilation are the characteristics of dilated cardiomyopathy. A group of scientists was able to derive iPSCs from patients with familial dilated cardiomyopathy. These patients had a point mutation on a sarcomeric protein that encodes a gene named troponin-T (R173W) (Sun, 2009). There is an abnormal regulation of altered calcium, decrease of contractility and abnormal distribution of α-sarcomeric actinin. Treatment with the help of overexpression of Serca2a or beta blockers can help in improving these structural and functional changes in the iPSCs derived from dilated cardiomyopathy patients. One of study worked on establishing iPSCs which were patient specific for the catecholaminergic polymorphic ventricular tachycardia disease model and this disease has characteristics of sudden cardiac death, ventricular arrhythmias and bad handling of calcium. These iPSCs help in the treatment of many cardiovascular problems and is one of the novel approaches to assess therapies and human disease mechanism understandings.

ROLE OF IPSCS IN ISCHEMIC CARDIOMYOPATHY:

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Left ventricular systolic dysfunction is caused by the great loss of mass of cardiac cells caused by myocardial infarction in ischemic cardiomyopathy. There are many methods of suppressing arrhythmia in ischemic heart including cardiomyocytes derived from embryonic stem cells and stem cells derived from bone marrow (Clifton-Brown et al., 2019). Studies have revealed that cardiomyocytes derived from iPSCs have a lower rejection due to immune system and there is enhanced survival rate as well. Cardiovascular cell sheets have been developed by combining with vascular cells derived from iPSCs and their transplantation in models of rat with myocardial infraction have shown some great progress. There are studies that showed that the iPSCs derived endothelial cells had great ability of improving the perfusion of ischemic tissue in mouse models with arterial disorder. Both in vivo and in vitro differentiation of cardiovascular lineages are possible with progenitor cells derived from iPSCs having a surface marker of Flk-1 (fetal liver kinase-1). These cells having marker of Flk-1 have been proved to have great results in improving the neo-vasculo-genesis and cardiac function when these were transferred into mice models heart having myocardial infraction. There is a study which showed the development of three-dimensional cardiac tissue patches with the help of cardiomyocytes derived from iPSCs and ESCs. These patches were engrafted into athymic rats' heart (Tulloch et al., 2011). The pattern of gene expression of cardiomyocytes derived from human iPSCs were more closely related to fetal cardiomyocytes as compared to that of adult cells. A preclinical study of iPSCs based therapy of cardiac cells showed that the iPSCs survived after transplantation and was also able to form a premature myocardium as well (Cappelleri et al., 2014). Damage caused due to ischemic injury have been shown to be repaired by using cells derived from iPSCs in these studies.

ROLE OF IPSCS IN GENE CORRECTION TECHNOLOGY

Gene correction is of the major application of this iPSC technology in cardiovascular problems. These iPSCs which are patient specific can be derived from patients by the help of non-viral methods from the patients with a cardiovascular disorder. These iPSCs can later be used for the purpose of gene correction with the help of CRISPR/Cas9 or TALENs (transcription activator-like effector nucleases) system. There was an attempt at first ever gene therapy in a mouse model having a humanized form of sickle cell anaemia with the help of iPSCs. These mice having sickle cell anaemia were able to be rescued with the help of transplanting hematopoietic progenitor cells which were collected from autologous iPSCs in this study. Cardiomyocytes derived from human iPSCs have been developed with expression of adenovirus and coxsackievirus receptors (Sharma et al., 2014). The antiviral drug efficacy was predicted by using such cardiomyocytes as they are susceptible to coxsackievirus infection. Demonstration of pathogenicity of patient specific iPSCs have been done by the help of CRISPR/Cas9 gene editing technology (Galluzzi et al., 2018). There are many advancements made in this field of iPSCs and correction of genes but still there are many problems like long-term risk factors, wider variety of application and off-target effects of mutations in cardiovascular area.

DRUG DEVELOPMENT AND IPSCS

There is advancement in generation of cardiomyocytes derived from iPSCs with the help of some non-viral methods has helped in many areas such as toxicity screening and drug development processes as well. These advancements have allowed for the development of many diseases specific iPSCs having phenotypes specific to that of patients by which both novel therapeutics and well-established drugs can be looked-up and screened for toxicity and efficacy as well (Samanta et al., 2018). This technology can also help in optimization of doses based on state of patient's disorder and other pharmacological effects of drugs. This technology of iPSC can greatly improve the safety of patients along with reduction of cost by having the ability of predicting cardiotoxicity and adverse reaction of drugs. Studies have showed the useof this technology in elucidation of electrophysiological and biochemical cardiotoxicity which was not possible earlier. There are reports which showed the use of cardiomyocytes obtained from human iPSC and these were able to detect the drug changes accurately in Ca2+ transient dynamics which can be helpful in prediction of drug induced arrhythmogenic liabilities in early detection of drug discovery phases (Murphy et al., 2018). These iPSC based cardiac models can help in understanding the molecular basis of toxic effects of various cardiac problems and help in re-engineering the systems to circumvent cardiotoxicity.

FUTURE PERSPECTIVES

As iPSCs are greatly responsive towards drugs, many pharmaceutical industries can use them conveniently for electrophysiological screening of

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drug of such cells. iPSCs which are patient specific, and cardiomyocytes derived from such cells are very important for the modelling of disease which can give more information for personalized medication and can be vastly useful for researchers for confirmation of responsiveness of new drugs or their effects can also be studied. One of the promising futures of these iPSCs is in the field of targeted modification of genes for repairing the mutations caused by disease (Collin and Lako, 2011; Garber et al., 2012). The pathology and the molecular mechanisms of evolution of disease can be understood greatly with the use of iPSC lines. There are reports of CRISPR/Cas9 plasmid which was used for correction of a point mutation in iPSCs and for obtaining an isogenic line of iPSCs (Grobarczyk et al., 2015).
This method of correction for iPSCs can be used in the future for their utilization in gene therapy. There are many barriers that needs to be overcome for a successful translation of iPSC technology for various disorders including cardiovascular and neurological problems. There is a need to improve the methods for enhancing the efficacy of non-viral reprogramming. There are many groups that are working greatly in this field using novel methods including throughput screening of efficiency-enhancing small molecules. There are many non-viral methods which have been used for the isolation of various iPSCs homogenous populations for their large-scale production on both commercial and clinical levels. Another important task is the selection of appropriate population of patient which are suited for iPSC-based therapy. The important concern includes complication of the disease, co-morbidities, and availability of alternate therapies.

CONCLUSION

Stem cells have been studied greatly in recent years and their use in medical field has been elaborated. The use of MSCs has been restricted due to ethical problems. These problems were the biggest drawback in the use of this technology. There was great research done in this field and scientists were able to obtain iPSCs from fibroblasts and many other cells. These iPSCs have the ability to divide into any type of cells and they also covered the ethical problems. Their discovery opened a new gateway of research and many advancements have been made in this field. Some of the major health problems includes cardiovascular and neurological problems which are normally very difficult to treat with conventional methods. The discovery of iPSCs allowed health care workers to test these cells in regenerative therapies and treat these disorders. Many successful results have been obtained with the use of these iPSCs against such disorders as mentioned above. Cardiovascular problems lead to the death of many people around the globe due to bad treatment methods and other side effects of conventional drugs. These problems were overcome by the use iPSCs for generation of specific types of cells and tissues which are lost during such problems and can be used for Repairing such problems.

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