Stem Cell Transplant Immunology

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Katharine K. Miller and Sonja Schrepfer

Abstract

Stem cell transplantation is quickly developing as an attractive therapeutic option for regenerating tissues injured by cardiovascular disease. From embryonic to induced pluripotent stem cells, from injection of stem cells to differentiation of cardiac cell lineages, researchers continue to push the boundaries of how stem

K.K. Miller
University Heart Center Hamburg, Transplant and Stem Cell Immunobiology (TSI)-Lab, Martinistrasse 52, D-20246 Hamburg, Germany

Department of Surgery, Transplant and Stem Cell Immunobiology (TSI)-Lab, University California San Francisco (UCSF), 513 Parnassus Avenue, Medical Sciences S1207, San Francisco, CA 94143, USA

Cardiovascular Research Center (CVRC), University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

German Centre for Cardiovascular Research (DZHK) e.V., University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany
e-mail: kmiller@uke.de

S. Schrepfer (✉)
University Heart Center Hamburg, Transplant and Stem Cell Immunobiology (TSI)-Lab, Martinistrasse 52, D-20246 Hamburg, Germany

Department of Surgery, Transplant and Stem Cell Immunobiology (TSI)-Lab, University California San Francisco (UCSF), 513 Parnassus Avenue, Medical Sciences S1207, San Francisco, CA 94143, USA

Cardiovascular Research Center (CVRC), University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

German Centre for Cardiovascular Research (DZHK) e.V., University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

Department of Cardiovascular Surgery, University Heart Center Hamburg, Martinistrasse 52, D-20246 Hamburg, Germany
e-mail: sonja.schrepfer@ucsf.edu

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cells can be used in treatments. The major hurdle in the way of creating effective methods for tissue regeneration is immune rejection of transplanted materials; even undifferentiated stem cells can be recognized by the transplant recipients' immune system, limiting their survival and overall beneficial potential. Posttransplant rejection of cellular materials does not always follow the same immunological progression, and as such, different types of stem cells can be rejected through distinct immune pathways. Therefore, a strong understanding of the known mechanisms behind stem cell immunogenicity—including specific cases of embryonic and patient-specific stem cell rejection—is pivotal for researchers to develop more efficient therapeutics. The future of stem cell transplantation research lies in developing techniques that prevent immune recognition of transplanted cells or tissues and in generating ready-to-use stem cell lines that can be quickly and easily prepared for transplantation.

Abbreviations

ES	Embryonic stem
HLA	Human leukocyte antigen
IFN	Interferon
iPS	Induced pluripotent
MHC	Major histocompatibility complex
miHA	Minor histocompatibility antigen
NK	Natural killer
NT-ESC	Nuclear transfer embryonic stem cell
TCR	T cell receptor
SCNT	Somatic cell nuclear transfer
SNPs	Single nucleotide polymorphisms

12.1 Stem Cell Therapy: Possibilities and Drawbacks

Stem cell therapy is fast developing as one of the most intriguing prospective treatments for regenerating injured cardiovascular tissue. With the low availability of organs for transplantation and the accompanying lengthy wait, the possibility of regenerating tissue by transplanting readily available cell lines into patients is understandably appealing. Stem cell therapy has shown promising initial results for rehabilitating ischemic heart tissue after transplantation in animal models (Yang et al. 2002; Laflamme et al. 2007; Nelson et al. 2009; Carpenter et al. 2012; Zwi-Dantsis et al. 2013); however, the propensity for the transplant recipient's immune system to reject allogeneic material greatly reduces the potential efficacy of therapeutics and diminishes the possible positive effects surrounding such treatment.

Because pluripotent stem cells can be differentiated into numerous cell types, the potential application of stem cell therapy is wide-ranging. Differentiation can be

performed ex vivo, allowing researchers or clinicians to closely monitor the procedure, insuring that the proper population of cells is generated prior to transplantation. In most cases, undifferentiated stem cells are avoided in clinical transplant therapies due to their propensity to form teratomas (Blum and Benvenisty 2008); rather, such therapies tend to use differentiated stem cells (e.g., stem cell-derived cardiomyocytes transplanted into the myocardium of patients suffering from heart failure).

Pluripotent stem cells can be obtained through a range of methods, from directly using embryonic stem cells, to generating induced pluripotent stem cells, and to performing somatic cell nuclear transfer. Designing more effective treatment options requires knowledge of the pros and cons behind each of the stem cell varieties, as well as the immunological reasons behind posttransplant rejection of pluripotent stem cells and their differentiated progeny. Researchers are working to design stem cell lines and transplantation methods that will not trigger rejection from the recipient's immune system. Until then, scientists continue to develop more efficacious therapeutics by avoiding materials that strongly induce immunological rejection pathways.

12.2 Immunological Mechanisms of Stem Cell Rejection

Transplanted materials—including stem cells—are easily rejected by the recipient's immune system. While acute cellular rejection can be successfully avoided through the use of general immunosuppressants, this treatment is not an ideal solution for long-term clinical applications as it can result in negative side effects (see Sect. 12.5.1). New methods must be developed in order to generate therapies that are conducive to robust cellular regeneration and the enduring health of transplant patients. In order to generate stem cell transplantation methods that effectively evade activation of the immune system, it is pivotal to understand the molecular mechanism behind their posttransplant rejection.

12.2.1 Major Histocompatibility Complexes

The immune system is designed to protect the individual from invading materials; the properties of the immune system that create effective protection are also the reason why allogeneic transplanted material is so effectively rejected. T lymphocytes continuously search for invading material and can recognize cells presenting antigens bound to major histocompatibility complexes (MHCs) at the cell surface (For reviews, see Horton et al. 2004; Neefjes et al. 2011). MHCs—human leukocyte antigens (HLAs) in humans—are cell surface molecules organized into two classes. Class I MHCs consist of three subunits and interact with a β2-microglobulin subunit, while class II MHCs are made up of four subunits and have no β2-microglobulin interaction (Fig. 12.1). MHC classes are also expressed in different cell types: class I MHCs are nearly ubiquitously expressed on cells with nuclei, and class II MHCs

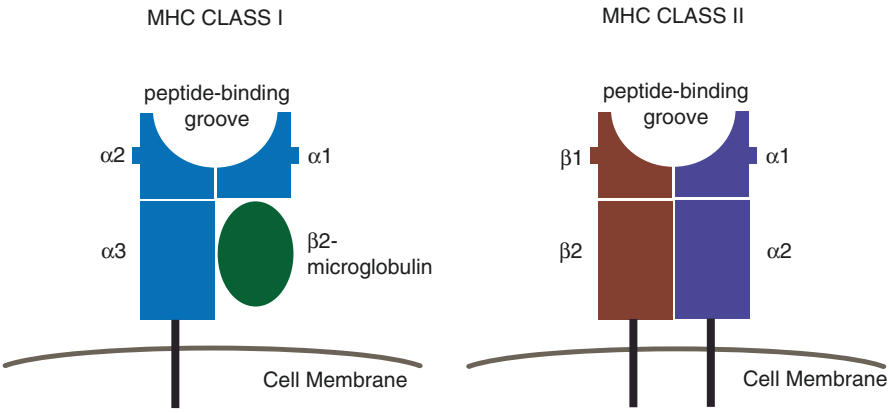

Fig. 12.1 MHC classes. Both MHC classes are membrane-bound complexes. MHC class I consists of three subunits which associate with a β2-microglobulin. MHC class II consists of four subunits. Both MHC classes contain a peptide-binding groove where antigen peptides can be presented

are found on so-called "antigen-presenting" cells, such as endothelial cells, macrophages, B cells, and dendritic cells. This separation in localization helps to ensure that the appropriate receptor can recognize the correct MHC class. When an antigen is taken into the cell, it is broken down into peptides. MHCs bind to certain frequently occurring peptide sequences and present them on the cell surface, at which point T cell receptors (TCRs) can interact directly with the MHC and peptide complex. The presence of the peptide bound to the MHC is necessary for this interaction and ensures that self-MHCs alone do not trigger a T cell reaction. TCRs are selected to recognize and avoid reacting to self-MHC variants without peptide or with self-peptide (Starr et al. 2003).

MHCs are polygenic: every individual carries multiple genes that influence the molecular makeup of their MHCs (Fig. 12.2). Each human individual carries six MHC class I alleles and 6–8 MHC class II alleles. Through this diversity, multiple different class I and II MHCs can be generated (Horton et al. 2004). Each polygene-specific MHC variant targets distinct subsets of peptide sequences, which allows immune detection of diverse antigens. Increasing the number of MHC-associated polygenes would expand the number of total peptides recognized by the varied final MHCs, which begs the question why MHC variations are relatively limited in individuals. One possible explanation relies on the fact that TCRs that can bind to and recognize self-MHCs without peptide should not be expressed. By increasing the number of MHC variants, there would have to be a corollary reduction in T cell diversity in order to prevent T cells attacking self-cells. The immune system seems to have struck a balance between the diversity of MHCs that can bind to various peptide sequences and the variety of T cells that can target antigen-bound MHCs.

Although MHC polygenes found in individuals are limited in number, the chance of infectious disease spreading throughout a population is low due to the polymorphic nature of MHCs (Fig. 12.2). Different MHC genes are expressed in individuals

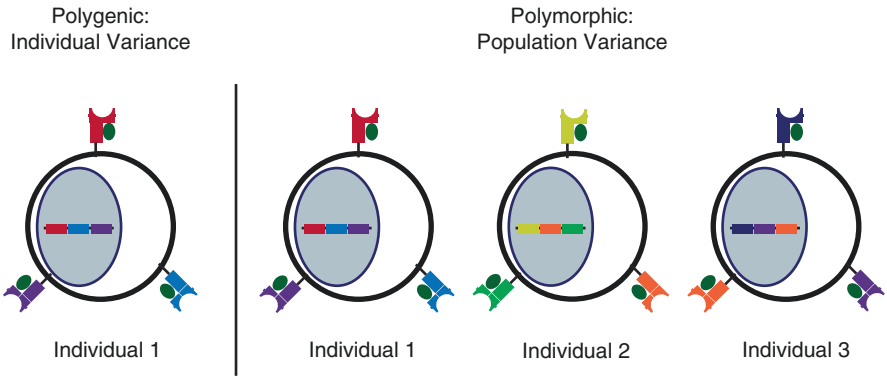

Fig. 12.2 MHCs are polygenic and polymorphic. Diversity of MHCs is generated through two methods. Diversity within the individual is generated through the polygenic nature of MHCs, with multiple genes coming together to form variants of MHCs. A broader diversity is generated population-wide through the polymorphic nature of MHCs. Different individuals often express different MHC genes, thereby increasing the overall number of peptides that can be bound and decreasing the chances for a population-wide epidemic

across the population, which allows the balance of MHC diversity and T cell diversity in the individual to be maintained while still generating an extremely diverse overall variety of peptide recognition in the population.

While the population-wide polymorphic nature of MHCs is very successful in preventing the human population from being wiped out by disease, it vastly complicates the matter of cellular, tissue, and organ transplantation. Allogeneic transplanted materials usually express different MHCs than the recipient. This causes transplanted materials to be identified as foreign invaders by the recipient's T cells. TCRs recognize specific self-MHCs bound to peptides, and they have been "trained" not to respond to self-MHCs without foreign antigen peptides. However, T cells can respond to non-autologous MHCs through a cross-reactivity process. This method for recognizing and reacting to mismatched MHCs is extremely important for the immune system to prevent invading material from attacking the host (Zerrahn et al. 1997; Macedo et al. 2009) but also complicates transplantation therapeutics.

12.2.2 Minor Histocompatibility Antigens

If MHCs were the only reason for immune rejection, MHC-matched transplantable materials would easily address this problem. However, even when using MHC-matched materials, posttransplant immune responses have still been observed (Goulmy et al. 1976; Vogt et al. 2000). Rejection can be caused by expression of minor histocompatibility antigens (miHAs). Simply, miHAs are altered peptides created from a small gene variance between individuals in a population. MHCs can bind to and present miHAs for recognition by T cells.

Most miHAs are generated by single nucleotide polymorphisms (SNPs), leading in some instances to alterations of a single amino acid within the encoded polypeptide according to the RNA codon usage. This change can potentially alter the structure and function of the protein and can even create a truncated isoform if a stop codon is produced upstream. Other mutations, such as gene deletions, can also generate miHAs. The final outcome in all cases is a small difference in the protein that is expressed between the donor and the recipient that, when presented by MHCs, can directly activate T cells. This alloantigenic property is the defining factor of miHAs.

The first reported miHA-caused rejection was identified after an HLA-matched male to female sibling transplantation rejection occurred. In this case, the presence of a miHA found on the Y chromosome increased T cell production and caused immune rejection (Goulmy et al. 1976). This study emphasized that certain rejection pathways can be activated despite controlling for matched MHCs and suggested that additional non-MHC-dependent transplant rejection pathways may exist.

In addition to Y chromosomal miHAs, several autosomal miHAs have been identified. Although the number of genes that could potentially generate miHAs is quite high, it appears that only certain gene alterations trigger recognition by the immune system. Even so, more than 50 different miHAs have been identified in humans, with more that likely exist (Table 12.1; Spierings 2014).

Table 12.1 More than 50 minor H antigens have been identified. While many antigens have the possibility to be minor H antigens, to date, around 50 minor H antigens have been identified (Spierings 2014)

Name	Gene
ACC-1Y	BCL2A1
ACC-1C	BCL2A1
ACC-2	BCL2A1
ACC-4	CTSH
ACC-5	CTSH
ACC-6	HMSD
C19orf48	C19orf48
CD19	CD19
DPH1	DPH1
HA-1/A2	HMHA1
HA-1/B60	HMHA1
HA-2	MYO1G
HA-3	AKAP13
HA-8	KIAA0020
HB-1H	HMHB1
HB-1Y	HMHB1
HEATR1	HEATR1

Table 12.1 (continued)

Name	Gene
HER2	HER-2/NEU
LB-ADIR-1	TOR3A
LB-APOBEC3B-1K	APOBEC3B
LB-ARHGDIB-1R	ARHGDIB
LB-BCAT2-1R	BCAT2
LB-EBI3-1I	EBI3
LB-ECGF-1	TYMP
LB-ERAP1-1R	ERAP1
LB-GEMIN4-1V	GEMIN4
LB-LY75-1K	LY75
LB-MR1-1R	MR1
LB-MTHFD1-1Q	MTHFD1
LB-NISCH-1A	NISCH
LB-NUP133-1R	NUP133
LB-PDCD11-1F	PDCD11
LB-PI4K2B-1S	PI4K2B
LB-PRCP-1D	PRCP
LB-PTK2B-1T	PTK2B
LB-SON-1R	SON
LB-SSR1-1S	SSR1
LB-SWAP70-1Q	SWAP70
LB-TRIP10-1EPC	TRIP10
LB-WNK1-1I	WNK1
LRH-1	P2X5
P2RX7	P2RX7
PANE1	CENPM
SLC19A1	SLC19A1
SLC1A5	SLC1A5
SP110	SP110
T4A	TRIM42
TRIM22	TRIM22
UGT2B17	UGT2B17
UGT2B17	UGT2B17
UGT2B17	UGT2B17
UTA2-1	KIAA1551
UTDP4	ZDHHC12
ZAPHIR	ZNF419

Although mismatched MHCs are considered to be the clearest cause of post-transplant rejection, miHAs have also been shown to be involved. With regard to hematopoietic stem cell transplantation, mismatched miHAs increased the occurrence of graft-versus-host disease and strongly decreased the probability of

overall survival (Dzierzak-Mietla et al. 2012). Taken together, it becomes clear that known miHAs should be considered when designing transplantation therapeutics.

12.3 Embryonic Stem Cell Immunogenicity

Early developments in stem cell therapy revolved around the generation of the first human embryonic stem (ES) cell line (Thomson et al. 1998). These pluripotent cells can be obtained from the blastocyst stage of embryonic development and not only have the ability to self-regenerate but can also be differentiated into various cell types. Despite ethical concerns and consequent restrictions on their availability, the unique properties of ES cells have been integral to many important research and clinical developments.

Initial reports suggested that ES cells were afforded a level of immune privilege, largely thought to exist due to their low levels of MHC expression (Li et al. 2004; Drukker et al. 2002). It was hoped that due to their immune privilege, ES cells could be transplanted into patients without triggering an immune response. However, over time it has become clear that the concept of ES cell immune privilege is more nuanced. Although some ES cells express low levels of MHCs, these MHC expression levels seem to be enough to trigger an immune response (Swijnenburg et al. 2008a; Deuse et al. 2011). Moreover, MHC levels appear to be highly variable and to change with regard to culture time, differentiation state, and culture conditions (Drukker et al. 2002).

An example of variable MHC expression levels on ES cells can be seen after the addition of interferon (IFN)-γ, a cytokine associated with transplantation and rejection (Drukker et al. 2002). Experimental addition of IFN-γ increased expression levels of MHC-I in undifferentiated ES cells, although a similar increase is not seen after addition of IFN-α or IFN-β. However, when ES cells are differentiated, all three IFNs can cause increased expression of MHC-I. This suggests that an increase in ES cell MHC expression could occur posttransplantation, therefore initiating rejection of cellular material.

Even without MHC expression level variation, ES cells may not avoid rejection. The "missing self" hypothesis suggests that cells that present low levels of MHC-I are more likely to be targeted by natural killer (NK) cells. NK cells use an inhibitory feedback loop to prevent an attack when they recognize MHCs (Karlhofer et al. 1992; Kambayashi et al. 2001). When MHC-I is not presented on a cell, the inhibitory pathway of NK cells is not activated. NK cells can then target low MHC-I-expressing cells as invading material. Indeed, during a syngeneic transplant model, it was shown that low levels of MHC-I resulted in a nearly total destruction of the graft by NK cells (Ma et al. 2011). However, when IFN-γ was added to the cells to induce MHC-I expression, the NK attack was mitigated. It appears that a delicate balance of MHC expression in stem cells during development is maintained in order to avoid triggering an immune response.

It has been suggested that an inability to easily resolve rejection during experiments over time is the culprit for varied reports on the immune privilege (or lack thereof) of ES cells. This was addressed by monitoring human ES cell survival through noninvasive bioluminescence, which further confirmed the progression of human ES cell rejection in a xenotransplant model. When posttransplant human ES cell survival was compared in immunocompetent and immunodeficient mice, it was shown that ES cell rejection was much higher in the immunocompetent mice (Swijnenburg et al. 2008b). Additionally, upon repeat injection of human ES cells, the rejection speed increased, suggesting that rejection was promoted by the adaptive immune system.

There has been particular interest in using stem cells to regenerate injured tissue, and ES cell's suggested immune privilege made them an ideal starting material for this research. ES cells can be differentiated in vitro into beating cardiomyocytes (Mummery et al. 2002; Xu et al. 2002; He et al. 2003), and initial transplantation of ES-derived cardiomyocytes into mouse cardiac tissue showed promise, with reports of integration and partially improved heart function (Laflamme et al. 2007; Ardehali et al. 2013). However, combined with the inclination for ES cells to form teratomas, there have been reports that ES-differentiated cardiomyocytes can induce an immune response in the myocardium posttransplantation (Nussbaum et al. 2007).

The first trial of human ES cell transplantation into humans has been undertaken with regard to regenerative therapy for patients with macular degeneration (Schwartz et al. 2012; Schwartz et al. 2015). The eye is a known immune privileged organ, which naturally reduces the possibility of posttransplant rejection (Streilein 2003). In this trial, retinal pigment epithelium was derived from human ES cells and transplanted into the subretinal space. Impressively, even nearly 2 years after treatment, a continued significant improvement in visual acuity was observed in the eyes that received the transplant. This was not accompanied by obvious safety issues. Future trials will surely look into methods to further improve regeneration, as well as hopefully moving ES cell therapy, toward the ability to regenerate additional tissue types.

ES cell therapy shows great promise for use in tissue regeneration. With varied reports of MHC expression level and immune responses, it is important that future studies not take ES cell immune privilege for granted. The immunogenicity of pluripotent stem cells remains one of the major hurdles in the way of developing effective clinical stem cell applications.

12.4 Patient-Specific Stem Cell Immunogenicity

Because allogeneic material is frequently and easily rejected, developing syngeneic and autologous stem cells has been a clear goal for generating better stem cell methodology. Subsequently, multiple methods for generating such cell lines have been

established, including induced pluripotent stem (iPS) cell and somatic cell nuclear transfer (SCNT) derivation. Both of these powerful technologies have been important for modern stem cell research development. However, despite their ability to generate genetically identical cellular material for transplantation, neither stem cell type fully avoids the problem of posttransplant immune rejection.

12.4.1 Induced Pluripotent Stem Cell Immunogenicity

Due to the ethical questions associated with ES cell use and the resulting restricted availability of ES cell lines, the research community welcomed the advent of iPS cells in 2006 (Takahashi and Yamanaka 2006). iPS cells are pluripotent cells generated through systematic reprogramming of adult cells by sequentially adding multiple chemicals or molecules. Once generated, iPS cells can be differentiated into many different cell lineages for research or clinical purposes.

Patient-specific differentiated cells have been targeted for their possible therapeutic applications through direct transplantation or generation of tissue grafts. Since these cells would be genetically identical to the donor recipient, it was initially believed that there would be no cause for the recipient immune system to recognize and reject them posttransplantation. However, it appears that even with a genetically identical template, patient-specific iPS cells may not always successfully avoid rejection.

Through the process of reprogramming autologous iPS cells, certain gene expression levels are increased when compared with ES cells. This altered gene expression can be recognized by the transplant recipient's immune system (Zhao et al. 2011; de Almeida et al. 2014). It may be that some of the overexpressed genes are normally turned off during development of the fetus' immune system. In the case of autologous iPS cells, their expression appears to cause the immune system to identify them as nonself cells (Fig. 12.3). A separate study found that T cell intrusion and tissue necrosis accompanied teratoma formation when autologous human iPS-derived cells were transplanted into a humanized mouse model. Moreover, depending on the type of cell derived from the human iPS cells, the level of immune response and accompanying rejection was altered (Zhao et al. 2015).

Despite difficulties with posttransplant rejection, iPS cells and iPS cell-derived cardiomyocytes continue to be a focal point for myocardial regenerative therapy. This is due in part to the fact that iPS cells can be proliferated in culture and differentiated into multiple cardiac cell lineages. Initial results have been encouraging in animal models, showing partial rescue of cardiac function (Nelson et al. 2009; Carpenter et al. 2012; Zwi-Dantsis et al. 2013). However, it seems that the number of cells that survive posttransplantation reduces significantly over time—a process that could have multiple explanations, including an immune response (Templin et al. 2012). Clearly, the immune reaction to iPS cells will have to be investigated in detail before their use in clinical applications.

Autologous-generated iPS cells for human treatment may not be ideal even if immune rejection can be avoided, since generating patient-specific iPS cells is

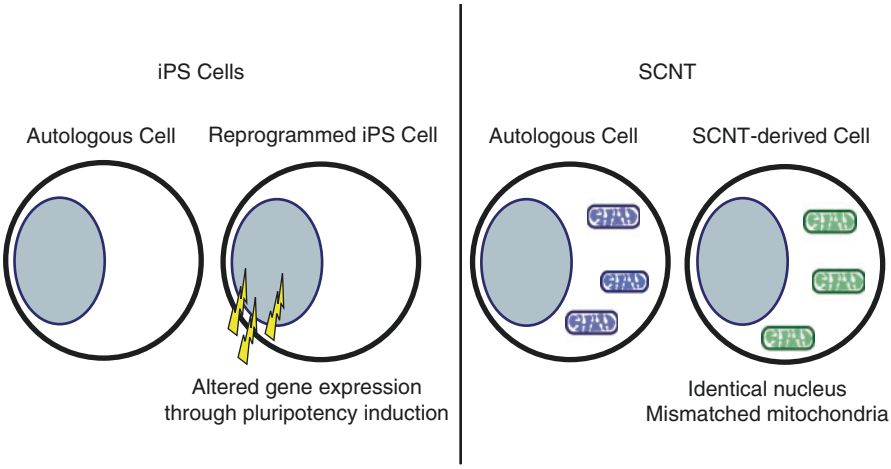

Fig. 12.3 iPS and SCNT cell immunogenicity. iPS cells can be generated to be autologous, which should prevent their rejection in theory. However, during this reprogramming, iPS cells may have altered expression of certain genes, which can cause rejection of transplanted cells. SCNT was suggested as an alternative method for generating cells with identical nuclei to the transplant recipient. However, mismatched mitochondrial DNA and consequent proteins appear to be enough to trigger rejection

extremely time, cost, and labor intensive. Speed of treatment is particularly necessary when responding to many types of cardiovascular disease. On the other hand, immune rejection of allogeneic iPS cells and iPS cell-derived cardiomyocytes undoubtedly inhibits their full regenerative potential. The ideal solution would be to create a method that could reliably reduce posttransplant rejection of allogeneic cells. If this can be achieved, an "off-the-shelf" iPS cell line or its derivatives could be kept on hand for fast response in cardiovascular disease therapy. Multiple laboratories worldwide are currently pursuing such technologies.

12.4.2 Somatic Cell Nuclear Transfer Immunogenicity

SCNT has been suggested as a method for quickly generating patient-specific stem cells (Tachibana et al. 2013). By transferring the nucleus from a patient cell into the cell body of an enucleated oocyte, the resulting pluripotent stem cell will contain an identical nuclear genome to the donor recipient. This was suggested as a potentially useful therapy for patients with mitochondrial disease, as the mitochondria are derived from the healthy oocyte donor (Tachibana et al. 2013).

While SCNT transfer has been successfully performed and used for significant stem cell research contributions, Deuse et al. found that despite generating matching nuclear genomes between the SCNT cells and the recipient, the mismatched mitochondria can stimulate an immune response due to differences in the mitochondrial DNA (Fig. 12.3; Deuse et al. 2015). Observation of embryonic stem cells

generated by nuclear transfer (NT-ESC) revealed that mismatched mitochondrial proteins are able to trigger the recipient immune system, even with as few as one or two mismatched proteins. The immune response appeared to be adaptive in nature, directed against mitochondrial content, and amenable for tolerance induction (Deuse et al. 2015).

iPS cell and SCNT technology continue to be extremely important for developing new regenerative therapies; however, it is clear that posttransplant rejection is a serious issue. For future development of stem cell therapies, it will be particularly important to keep in mind the possible immunogenic effects of proteins associated with pluripotency and mismatched mitochondria.

12.5 Current and Developing Methods to Reduce Stem Cell Immunogenicity

The future of stem cell therapy relies on developing methods that can regenerate tissue without activating an immune response. Finding a method that can overcome this hurdle is one of the "holy grails" of modern cardiovascular disease research. Some methods, such as general immunosuppression, while not ideal, are presently in use to prevent rejection of transplanted materials. However, many innovate techniques are currently under development.

12.5.1 General Immunosuppression

Since there are many nuanced reasons why immune rejection of transplanted stem cells can occur, the research community will have to be innovative with regard to developing therapeutic methods. Currently, one of the main methods used to prevent posttransplant rejection is through long-term use of general immunosuppressants, including corticosteroids and calcineurin inhibitors such as cyclosporine or tacrolimus. However, use of long-term immunosuppressants is not an ideal solution, as it can lead to severe side effects including cardiovascular complications, infections, and increased risk of cancer, among others (Hsu et al. 2008; Khurana and Brennan 2011). Finding methods that prevent the rejection of transplanted material without compromising the general immune system would be better alternatives.

12.5.2 Cardiospheres

The recent generation of cardiospheres and cardiosphere-derived cells has shown promise as a method for therapeutic regeneration. Cardiospheres are cells derived from the heart that have stem capabilities, in that they can be differentiated into different cell lineages and can regenerate (Messina 2004). Importantly, autologous cardiosphere-derived cell transplantation was clinically tested through a trial named CADUCEUS (Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular

Dysfunction) (Makkar et al. 2012). The CADUCEUS trial monitored tissue regeneration and overall health in patients that had a recent myocardial infarction. Although they did not find any improvements in cardiac function, they did observe a reduction in myocardial scarring. The current ALLSTAR (Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration) trial is assessing for the first time the safety and efficacy of allogeneic cardiospheres as a treatment option for patients within 12 months of a myocardial infarction (Makkar et al. 2014). Use of cardiospheres for tissue regeneration shows promise; however it will be important to identify the mechanism by which cardiosphere cells act as well as methods for increasing treatment efficacy.

12.5.3 Generation of a Molecularly Modified Stem Cell Line

One method to avoid immune rejection would be to create a molecularly modified non-immunogenic stem cell line. Such an "off-the-shelf" cell line would be very useful for clinical stem cell therapy in regenerative medicine. This cell line might be created by altering the expression levels of different molecules (e.g., MHCs) in order to modify the cell's communication and interaction with T lymphocytes, NK cells, and macrophages. However, one complication with such a method is that mismatched MHCs are targeted by T lymphocytes. Generating multiple "off-the-shelf" stem cell lines that express various MHC molecules could solve this problem. The number of MHC cell variants needed for a comprehensive cell bank for human treatment has previously been calculated, and while it varies between populations, it remains within a reasonably maintainable range (Taylor et al. 2012).

A second major complication with generating a non-immunogenic stem cell line is that certain stem cell molecular markers (e.g., OCT4) appear to strike a delicate balance between conferring stem abilities and causing cancer (Chiou et al. 2010). Because of this, most humans develop T cells against these markers in abundance, which may be necessary in adults to prevent cancer development. If generation of a non-immunogenic stem cell line relies on reducing the recognition of stem cell molecular markers, this may result in an increase in cancer development. Generation of a molecularly modified stem cell line that does not induce immune rejection or generate cancer will not be a simple undertaking, but if such a cell line could be achieved, it would be a game changer for stem cell therapy.

12.5.4 Creating a Local Hypo-immunogenic Environment

As indicated in Sect. 12.5.1, general immunosuppression can cause multiple negative long-term consequences for patients. A method that could generate a local hypo-immunogenic environment and suppresses the immune system only at the site of transplantation would be a prodigious alternative. A natural model for such a specific immune response reduction is found in fetomaternal tolerance (Guleria and Sayegh 2007). Because the fetus' genetic material is 50% paternally inherited and

therefore partially allogeneic to the mother, there are multiple mechanisms in the mother's body that prevent fetal rejection. Importantly, the mother's general immune system does not seem to be significantly affected under such circumstances. It may be possible to harness the natural methods of fetomaternal tolerance to create a local hypo-immunogenic environment for transplanted materials without affecting the general immune system of the patient.

12.5.5 Final Takeaway

Potential stem cell therapies continue to quickly develop, and many show great promise in the field of regenerative medicine. The ability to continuously and consistently generate new cells to replace malfunctioning, dead, or missing tissue is an advantage to using stem cells; however, as with any transplanted material, the propensity for posttransplant rejection has constrained the possible positive results of stem cell therapy. By avoiding known transplant rejection catalysts (e.g., by matching MHCs before transplantation or by keeping in mind the possible immunogenicity of mismatched mitochondrial proteins), current transplant techniques continue to increase in efficacy. Future methods to reduce immune responses to transplantation are under development and give hope for increased success of regenerative stem cell therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

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