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Review article

Application of induced pluripotent stem cell transplants: Autologous or allogeneic?

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ABSTRACT

The development of induced pluripotent stem cells (iPS cells) has raised the prospect of patient-specific treatments for various diseases. Theoretically, iPS cell technology avoids the limitations of human embryonic stem cells (ES cells), including poor establishment, ethical issues, and immune rejection of allogeneic transplantation. However, the immunogenicity of iPS cells has attracted the attention of researchers, and it remains unclear whether iPS cells and their derivatives will be recognized as a patient's own cells. Even though iPS-derived functional cells have been used in the treatment of some diseases, the process of somatic cell reprogramming and iPS cell differentiation is time-consuming, making it difficult to use iPS cells in acute illness or injury. In recent years, it has been suggested that iPS cells may be used as allografts by establishing an iPS cell bank and HLA matching, providing a novel strategy for the clinical application of iPS cells. This article provides a concise overview of iPS cell immunogenicity, and summarizes published data regarding the application of iPS cells in both autologous and allogeneic transplantation in order to help develop more reliable biotechnical strategies utilizing iPS cells.

1. Introduction

Induced pluripotent stem cells (iPS cells) are embryonic stem cell (ES cell)-like cells that are generated from somatic cells by the induction of defined transcription factors [1]. The iPS cells have similar characteristics to ES cells, such as unlimited self-renewal, and multilineage *in vivo* and *in vitro* differentiation to all three germ layers [2]. In recent years, methods to generate iPS cells have improved, and some non-integration methods were established to induce more safe iPS cells for *in vivo* transplantation [3–5]. In particular, small molecule compounds have a great potential for the process of iPS cell reprogramming [5–7].

In contrast to ES cells, iPS cells can be generated from a patient's own somatic cells, including fat cells, nerve cells, skin fibroblasts, cuticle cells, fetal foreskin cells, B cells, T cells, peripheral blood mononuclear cells, umbilical cord mesenchymal cells, chorionic mesenchymal cells, and amniotic mesenchymal cells [5–13]. As such, patient-specific iPS cells can be generated without ethical issues. Moreover, the proliferation and differentiation ability of iPS cells have been demonstrated to be similar to that of ES cells [14]. In addition, iPS cells are considered far more useful than ES cells because they are generated from a patient's own cells and thus there is theoretically no risk of rejection when administered to the same individual. However, it has been suggested that the immunogenicity of iPS cells could change during reprogramming and differentiation, resulting in immune rejection after autologous transplantation [15]. This issue has received a great deal of debate, and early on some researchers argued that the idea was ridiculous without any basis [16–18]. In fact, both iPS generation and differentiation required a series of artificial operations performed *in vitro*. A reliable evaluation system hasn't been established to evaluate the safety of these procedures, and it is possible that fatal errors or mutations can occur during these processes that change the cell

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immunogenicity which can lead to immune rejection [19–21]. In addition, the process of developing iPS cells from somatic cells is very time-consuming [22]. The length process limits the application of iPS cells in acute illnesses and injuries such as acute cerebral hemorrhage, trauma, acute heart failure, anaphylactic shock, gastrointestinal bleeding, acute gastroenteritis, and acute respiratory distress [23–25]. Some researchers have suggested developing an iPS cell bank for cell or tissue transplantation based on HLA type [26].

The purpose of this article is to provide a general overview of autologous and allogeneic transplantation of iPS cell-derived functional cells or tissues, and discuss strategies for the clinical application of iPS cells.

2. Immunogenicity of iPS cells and their derivatives

In theory, iPS cells and their derivatives shouldn't be immunogenic to the autologous or isogenic immune system. However, some studies have demonstrated that iPS cells can display genetic and epigenetic abnormalities because of their genomic instability, and thus elicit an immune response or tumorigenicity *in vivo* [27,28]. For example, some larger-scale studies identified an amplification of 20q11.21 as the most recurrent copy number variation in human iPS cells [29,30]. Furthermore, duplication of 20q11, enriched with different genes associated with anti-apoptosis and pluripotency, has been identified in several types of cancer cells [31,32]. It has also been noted that early-passage iPS cells from Sertoli cells formed more teratomas with less tissue damage, less immune cell infiltration, and less necrosis *in vivo*, compared with late-passage iPS cells in syngeneic mice, suggesting that the iPS cells may lose the low immunogenicity and be recognized by immune system after extended passaging *in vitro* [33]. Study has also shown that after the transplantation of mouse ES cells and fibroblasts-derived iPS cells, the teratomas formed by iPS cells are mostly immune-rejected by the recipients, while ES cell-derived teratomas exhibit more immune tolerance. Global gene expression analysis indicated an increase of several genes, including Zg16 and Hormad1, in iPS-derived teratomas, but not in ES-derived teratomas [18].

Of course, undifferentiated iPS cells are not used clinically because of the potential to randomly differentiate into teratomas and cause infiltration of immune cells [34]. As such, the immunogenicity of terminally differentiated cells derived from iPS cells is of clinical significance in the use of iPS cells. In 2013, Araki et al. examined the immunogenicity of mouse iPS- and ES-differentiated skin and bone marrow tissues *in vivo*, and found no obvious immune responses, including T cell infiltration, in tissues derived from either source. In addition, no increase in the expression of the immunogenicity-causing Zg16 and Hormad1 genes was observed [35]. However, in the Araki study, all of the differentiations were induced *in vivo* and thus do not accurately represent clinical therapies with human iPS cells. Other study performed *in vitro* differentiation of the three different germ layers, followed by transplantation *in vivo*. No evidence of increased T cell proliferation or other indicators of immune rejection were found after the transplantation mouse iPS-derived neuronal cells (ectoderm), endothelial cells (mesoderm), and hepatocytes (endoderm), supporting that autologous iPS-derived functional cells could be used for autologous transplantation without eliciting immune rejection [36].

However, all of the aforementioned studies were performed with rodent models and the results may not be applicable to primates, including humans. The first study using a monkey model to evaluate the immunogenicity of iPS cell-derived neural cells was performed in 2013 [9]. The transplantation of autologous iPS cell-derived neurons did not provoke an obvious immune response and the neurons survived well in monkey brain. In contrast, a strong immune rejection response was caused by allografts with infiltration of leukocytes and the activation of microglia in the brain tissue. In a subsequent study by our group, we further examined the immunogenicity of human iPS cells and their derivatives. We found that both somatic cells and iPS cell-derived neural progenitor cells did not stimulate the proliferation of autogenous peripheral blood mesenchymal cells (PBMC) *in vitro*. No increased expression of granzyme B or perforin was observed following stimulation of T cells and natural killer (NK) cells in the *in vitro* co-culture system. On the other hand, a significant immune reaction was detected when these immune effector cells were stimulated with the allogeneic iPS cell-derived neural progenitor cells [37]. In a similar study using a humanized mouse model, the teratomas formed by autologous human iPS cells induced the local infiltration of antigen-specific T cells as well as tissue necrosis. In addition, autologous iPS cell-derived smooth muscle cells were highly immunogenic in the humanized mouse, while autologous iPS cell-derived retinal pigment epithelial cells were not immunogenic. It is possible that the different immunogenicity is due to abnormal expression of some immunogenic antigens in smooth muscle cells [38].

Taken together, pre-clinical studies suggest that human iPS cell-derived functional cells or tissues do not initiate an obvious immune response during the process of autogenous transplantation. The first human evaluation of iPS-cells was performed in 2014. A patient's skin-derived iPS cells were differentiated into retinal pigment epithelium, which was then transplanted into the eye of the same patient, a 70-year-old woman with age-related macular degeneration [39]. There were no complications of the transplant surgery. After transplantation, the visual decline of the patient ceased, and remained stable without any medication. At 18 months postoperatively, the transplanted retinal pigment epithelial sheet was surviving well, and there was no evidence of immune rejection or adverse unexpected proliferation. Subsequently, a second transplantation of iPS cell-derived retinal pigment epithelium was attempted by the same group. However, genetic mutations were found in the patient's iPS cells and retinal cells, which might lead to some problems such as tumorigenic, and the procedure was not performed [39].

3. Potential of iPS cell-derived low-immunogenic functional cells/tissues in allografts

iPS cell-derived low-immunogenic functional cells or tissues hold great potential in the allogeneic transplantation of tissues such as cartilage [40] and retinal pigment epithelial cells [41]. Some researchers have induced human iPS cells to secrete and deposit cartilage extracellular matrix, and ultimately form cartilage tissue in three-dimensional culture environment. After the transplantation of iPS cell-derived cartilage tissue into joint surface defects in immunosuppressed minipigs, as well as immunodeficient rats, the transplanted cartilage survived and was gradually integrated into the native cartilage [42]. In addition, the iPS cell-derived cartilage expressed limited amounts of major histocompatibility complex, and didn't stimulate the proliferation of T cells or the activation of NK cells when co-cultured with mixed lymphocytes, suggesting that the iPS cell-derived cartilage is no more antigenic than normal human cartilage [43].

In addition to cartilage cells, iPS cell-derived retinal pigment epithelium cells, an immune-privileged cell, have been demonstrated to produce no significant pathological changes after transplantation *in vivo*. Furthermore, iPS cell-derived retinal pigment epithelium cells that integrate into the subretinal space outlive the photoreceptors and have been shown to survive for as long as two and a half years. However, the nonintegrating retinal pigment epithelium cells are ingested by host macrophages [41]. Overall, these findings indicate that iPS cell-derived low-immunogenic functional cells/tissues hold a great value for allografts.

In a previous study, we developed an alternate way to establish low-immunogenic cells from iPS cells. Human iPS cells were derived from umbilical cord mesenchymal cells and skin fibroblasts. They were then differentiated into neural precursor cells. After co-culture with allogeneic PBMCs, we found that after reprogramming and differentiation the genetic memory of cellular immunogenicity remained. The iPS cells