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MINI REVIEW

The immunogenicity of cells derived from induced pluripotent stem cells

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With their ability to undergo unlimited self-renewal in culture and to differentiate into all cell types in the body, human embryonic stem cells (hESCs) hold great potential for the treatment of currently incurable diseases. Two hESC-based cell therapies for spinal cord injury and macular degeneration have been advanced into human clinical trials. Despite this rapid progress, one key challenge of hESC-based cell therapy is the allogeneic immune rejection of hESC-derived cells by recipients. This problem could be mitigated by a recent breakthrough in the technology of induced pluripotent stem cells (iPSCs) by nuclear reprogramming of patient-specific somatic cells with defined factors, which could become a renewable source of autologous cells for cell therapy. However, recent studies revealing the abnormal epigenetics, genomic stability and immunogenicity of iPSCs have raised safety concerns over iPSC-based therapy. Recent findings related to the immunogenicity of iPSC derivatives will be summarized in this review.
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INTRODUCTION

Allogenic immune rejection is mediated primarily by T cell-dependent immune responses.[1] While the standard immune suppressant regimens have been used successfully to suppress allograft rejection, long-term administration of immune suppressants is highly toxic, especially to patients with chronic diseases. In addition, persistent systemic immune suppression leads to an increased risk of cancer and infection, further increasing the ratio of risk versus benefit of human embryonic stem cell (hESC)-based therapy. Therefore, to improve the feasibility of hESC-based therapy, new strategies must be developed to induce the immune tolerance of hESC-derived cells without causing systemic immune suppression. In this context, it may be possible to induce immune tolerance of hESC-derived allogeneic cells by disrupting the co-stimulatory pathways required for T-cell activation, such as the CD28-B7 and CD40–CD40L pathways.[2,3] In support of this notion, recent studies have shown that such modulation could protect the hESC-derived cells from allogenic human immune responses *in vivo*.[4] In addition, recent clinical data have demonstrated that hematopoietic chimerism that is established by the infusion of hematopoietic stem cells from a donor into a recipient can induce long-term immune tolerance of allografts from the same donor.[5,6] Therefore, another potential approach to induce the immune tolerance of hESC-derived allogeneic cells is to establish hematopoietic chimerism in the recipient using hematopoietic stem cells derived from the same hESCs. While this approach is promising, it remains a challenge to differentiate hESCs into functional hematopoietic stem cells that can efficiently reconstitute the human immune system *in vivo*.[7–9]

THE IMMUNOGENICITY OF INDUCED PLURIPOTENT STEM CELLS (IPSC)-DERIVED TERATOMAS

One key advantage of iPSCs for human cell therapy is that patient-specific iPSCs are autologous, and, therefore, it has been assumed that the cells derived from them can be transplanted into the same patient without concerns over immune rejection. However, in contrast to this general assumption, one recent study has used the inbred C57BL/6 (B6) mouse strain to demonstrate that cells differentiated from the B6 iPSCs within teratomas can be immunogenic in the syngeneic B6 recipient mice, raising concerns about the immunogenicity of iPSCs.[10] In support of this notion, and also relying on the B6 inbred mouse strain, Abe and colleagues[11] reported in *Nature* recently that cardiomyocytes differentiated from B6 iPSCs *in vitro* are highly immunogenic when transplanted into B6 mice. In the same report, however, the authors found that B6 iPSC-derived

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skin tissue obtained from chimeric mice generated by injecting B6 iPSCs into B6 blastocyts have negligible immunogenicity and are completely immune tolerated by B6 recipients.[11]

THE IMMUNOGENICITY OF IPSC-DERIVED TISSUES FROM CHIMERIC MICE

This chimeric mouse transplantation assay may not be suitable for studying the immunogenicity of iPSC-derived cells. While the skin tissue of GFP-expressing B6 mice will be immune rejected when transplanted into GFP-negative B6 mice due to the expression of the immunogenic GFP minor antigen,[12,13] it is quite surprising that B6 iPSC-derived GFP-expressing skin tissue is completely immune tolerated by the GFP-negative B6 mice in this study.[11] Therefore, if using this chimeric mouse transplantation system, the B6 iPSC-derived skin cells will be immune tolerated by B6 mice even if they express minor antigens, making it an inappropriate assay to evaluate the immunogenicity of iPSC-derived cells. It is likely that, during the development of the chimeric mice, the abnormal and immunogenic B6 iPSC-derived cells have been immune rejected or rendered immune tolerated by the B6 immune system present in the chimeric mice, before their subsequent transplantation into B6 recipients to evaluate whether immunogenicity is caused by minor antigens. In further support of this notion, while the study by Zhao *et al.*[10] demonstrates that the regressing teratomas formed by B6 iPSCs in B6 mice overexpress a panel of immunogenic proteins including Hormad 1 and Zg16, these immunogenic proteins are not overexpressed in the iPSC-derived tissues in the chimeric mice.[11]

THE IMMUNOGENICITY OF IPSC-DERIVED CELLS *IN VITRO*

In another recently published study using the B6 mouse transplantation system,[14] various types of cells differentiated from B6 iPSCs *in vitro* were transplanted to a site under the kidney capsule of B6 mice. In contrast to the findings of robust immune responses to B6 iPSC-derived cardiomyocytes grafted into the heart of B6 mice,[11] this study found no immune responses to various types of cells derived from B6 iPSCs that have been transplanted under the renal capsule. However, it is unexpected that even the cells derived from the viral vector-induced B6 iPSCs that are known to express immunogenic proteins such as Oct4 would be completely immune tolerated using this transplantation protocol. While subcutaneous transplantation allows extensive exposure of the grafted cells to functional dendritic cells (such as the Langerhans cells that are richly embedded in the skin and are the major antigen presenting cells crucial to present minor antigens of iPSC-derived cells), the dendritic cells in the kidney are of the immature type prone to inducing immune tolerance.[15,16] Therefore, the kidney capsule might not be an appropriate anatomic site in which to study immune responses to minor antigens.

CONCLUSION AND PERSPECTIVE

In summary, while mouse studies using different differentiation or transplantation protocols have led to inconsistent conclusions, these data support the notion that various cell types differentiated from iPSCs might have distinctive immunogenicities in their syngeneic hosts. It remains to be determined whether cells derived from iPSCs under other physiological conditions such as tetraploid complementation are immunogenic. In addition, to develop human iPSC-based therapy, it remains a challenge to evaluate the immunogenicity of cells derived from human iPSCs in the context of an autologous human immune system.

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