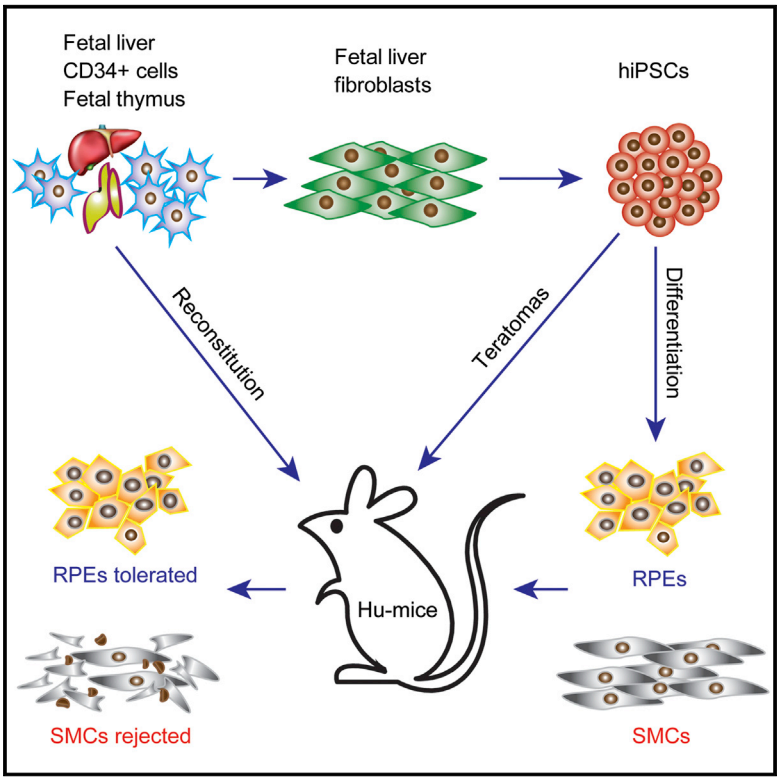
Short Article

Cell Stem Cell

Humanized Mice Reveal Differential Immunogenicity of Cells Derived from Autologous Induced Pluripotent Stem Cells

Graphical Abstract



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In Brief

Patient iPSCs have potential as a renewable source for autologous cell therapy that avoids immune rejection. Using a humanized mouse model with a functional human immune system, Zhao et al. observe differential immune responses to various autologous hiPSC derivatives, including rejection of smooth muscle cells and tolerance to retinal pigmented epithelium.

Highlights

- Hu-mice offer a model to study immune responses to autologous hiPSC derivatives
- Hu-mice reveal differential immune responses to hiPSC-derived SMCs and RPEs
- Misexpression of immunogenic antigens in hiPSC-derived SMCs leads to T cell response
- hiPSC-RPEs are tolerated even in non-ocular sites, supporting their clinical use

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Humanized Mice Reveal Differential Immunogenicity of Cells Derived from Autologous Induced Pluripotent Stem Cells

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SUMMARY

The breakthrough of induced pluripotent stem cell (iPSC) technology has raised the possibility that patient-specific iPSCs may become a renewable source of autologous cells for cell therapy without the concern of immune rejection. However, the immunogenicity of autologous human iPSC (hiPSC)-derived cells is not well understood. Using a humanized mouse model (denoted Hu-mice) reconstituted with a functional human immune system, we demonstrate that most teratomas formed by autologous integration-free hiPSCs exhibit local infiltration of antigen-specific T cells and associated tissue necrosis, indicating immune rejection of certain hiPSC-derived cells. In this context, autologous hiPSC-derived smooth muscle cells (SMCs) appear to be highly immunogenic, while autologous hiPSC-derived retinal pigment epithelial (RPE) cells are immune tolerated even in non-ocular locations. This differential immunogenicity is due in part to abnormal expression of immunogenic antigens in hiPSC-derived SMCs, but not in hiPSC-derived RPEs. These findings support the feasibility of developing hiPSC-derived RPEs for treating macular degeneration.

INTRODUCTION

The recent breakthrough in the generation of induced pluripotent stem cells (iPSCs) by reprogramming somatic cells with defined factors has raised the hope that iPSCs, which are identical to human embryonic stem cells (hESCs) in the context of pluripotency, could become a renewable source of autologous cells for transplantation into human patients (Lewitzky and Yamanaka, 2007). In addition, the disease-specific iPSCs could provide the unique opportunity to develop the much needed disease models in drug discovery. While it has been assumed that the immune rejection problem challenging hESCs could be mitigated by the development of patient-specific hiPSCs without the concern of immune rejection (Park et al., 2008; Takahashi et al., 2007; Yu et al., 2007), recent studies have shown that certain cell types derived from mouse iPSCs such as cardiomyocytes are immunogenic in syngeneic recipients, and other immunogenic cell types such as endothelial cells are immune tolerated by expressing high levels of immune-suppressive cytokines such as IL-10 (Araki et al., 2013; de Almeida et al., 2014; Zhao et al., 2011). Therefore, as an integral part of the effort to develop hiPSCs into human cell therapy, it is important to evaluate the immunogenicity of hiPSC-derived cells in the context of an autologous human immune system. To address this bottleneck, we established humanized mouse models that are efficiently reconstituted with both T and B cells as well as macrophages and dendritic cells required for antigen presentation (Figure S1A). As we recently published (Rong et al., 2014), these Hu-mice can mount vigorous immune rejection of allogeneic cells derived from hESCs (Figures S1B–S1E). Therefore, the Hu-mice provide a unique opportunity to examine the immunogenicity of autologous cells derived from hiPSCs.

RESULTS

Teratomas Formed by hiPSCs Are Immunogenic to Autologous Human T Cells

To generate autologous integration-free hiPSCs, fibroblasts were derived from the same human fetal liver used to reconstitute the human immune system in Hu-mice (Figure 1A). These cells were reprogrammed into integration-free hiPSCs with either the episomal approaches we previously described (Zhao et al.,