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Review
A Decade of iPS Cells

Molecular Obstacles to Clinical Translation of iPSCs

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The ability to reprogram somatic cells into induced pluripotent stem cells (iPSCs) using defined factors provides new tools for biomedical research. However, some iPSC clones display tumorigenic and immunogenic potential, thus raising concerns about their utility and safety in the clinical setting. Furthermore, variability in iPSC differentiation potential has also been described. Here we discuss whether these therapeutic obstacles are specific to transcription-factor-mediated reprogramming or inherent to every cellular reprogramming method. Finally, we address whether a better understanding of the mechanism underlying the reprogramming process might improve the fidelity of reprogramming and, therefore, the iPSC quality.

In 2005, we were in a lab retreat discussing how many genes would be required to reprogram somatic cells to pluripotency. No one suggested just four proteins. The following year, Takahashi and Yamanaka (2006) reported the generation of induced pluripotent stem cells (iPSCs) using a reprogramming cocktail of *Oct4*, *Sox2*, *Klf4*, and *Myc* (hereafter referred to as OSKM), a discovery that has undoubtedly changed the field of regenerative medicine and our understanding of cellular identity. iPSC technology is based on the assumption that a set of transcription factors expressed in embryonic stem cells (ESCs) is responsible for maintaining a pluripotent fate and is sufficient for establishing a de novo pluripotency program. Finding this specific combination of factors is an extraordinary accomplishment considering that ESCs express thousands of proteins. Nicely, the same cocktail of proteins was later shown to also reprogram human somatic cells to pluripotency (Takahashi et al., 2007). The beauty of this finding is that a simple experiment with a very low probability for success answered a complex question. We wonder whether Yamanaka received funding for this specific experiment, considering that many grants are awarded based on the probability of generating the expected results.

In the last 10 years, iPSCs have been thoroughly scrutinized, and their value as a disease model and a source of cells has been intensively debated. Indeed, genetic mutations and chromosomal aberrations detected in iPSCs have raised concerns about their tumorigenic potential (Yamanaka, 2012). Likewise, epigenetic aberrations have questioned iPSC differentiation potential and immune tolerance after autologous transplantation (Okita et al., 2011). However, further analyses have demonstrated that these abnormalities are mostly due to technical limitations, thus excluding these reprogramming errors as an intrinsic characteristic of transcription factor-mediated reprogramming. Here we review the immunogenic and tumorigenic features attributed to some iPSC clones, the relationship between these undesirable traits and incomplete reprogramming, and the mechanisms underlying different reprogramming methods as a strategy for improving iPSC reprogramming fidelity and thus the utility of iPSCs in molecular and biomedical applications.

Immune Response to Autologous iPSCs and Their Progeny

One of the main expectations of iPSC technology is to supply cells for autologous transplantation. Indeed, patient-specific iPSC derivatives have been assumed to be tolerated by the immune system, thereby evading life-long immunosuppressive treatment for the prevention of allograft rejection. Somatic cell nuclear transfer (SCNT) can also generate autologous pluripotent cells. However, SCNT ESCs retain the mitochondria from the recipient oocyte, which induce alloimmunity after transplantation in mice genetically matched to the reprogrammed nucleus (Deuse et al., 2015).

The high expectations regarding the immune tolerance of patient-specific iPSCs started to be questioned when Zhao et al. (2011) reported that the transplantation of iPSCs into syngeneic murine recipients led to the formation of immunogenic teratomas (Figure 1A). Those authors showed that iPSC-derived teratomas expressed a subset of antigens that were not detected in the teratomas generated after ESC transplantation and speculated that the expression of these aberrant antigens was due to the incomplete reprogramming of iPSCs (Zhao et al., 2011). These findings raised doubts about the practical applications of iPSC technology in cell replacement therapies. The main criticism of the report by Zhao et al. (2011) was that it assessed the immunogenicity of iPSC-derived teratomas rather than pure populations of iPSC-differentiated cells, which are the cells to be used for transplantation in medical treatments (Okita et al., 2011). To address this issue, Araki et al. (2013) generated iPSC-chimeric mice from which terminally differentiated tissues were isolated and subsequently transplanted into genetically matched recipients (Figure 1B). These in vivo-differentiated tissues showed limited immunogenicity; thus the authors conclude that iPSC derivatives do not elicit an immune response (Araki et al., 2013).

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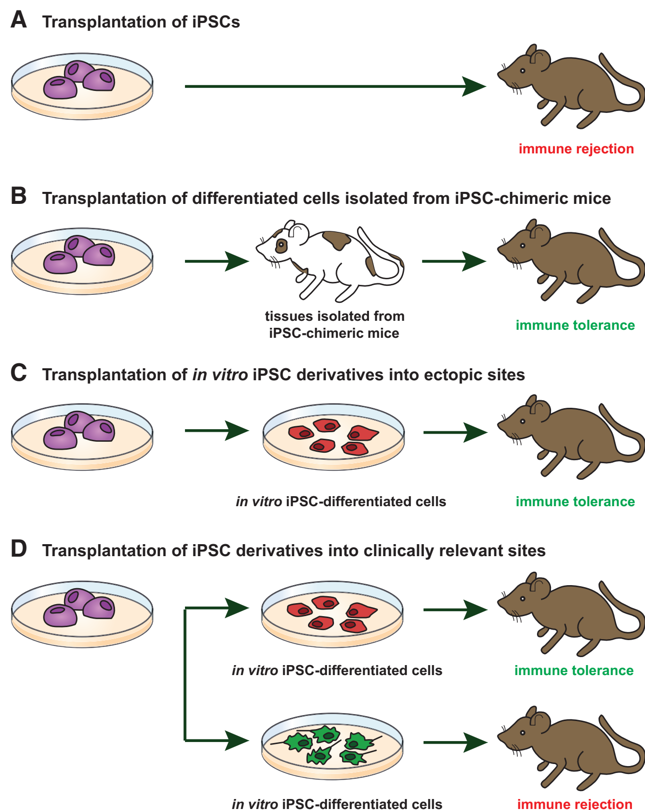

Figure 1. Immune Response to Autologous iPSCs and Their Progeny
(A) The subcutaneous injection of iPSCs into the hind leg of genetically matched mice was described to induce an immune response, which initially suggested that isogenic iPSCs might not be tolerated by the immune system (Zhao et al., 2011).
(B) Transplantation of terminally differentiated tissues isolated from syngeneic iPSC-derived chimeric mice into the skin and bone marrow of syngeneic mice was shown to elicit limited immunogenicity, demonstrating that iPSC-derived tissues are not immunogenic (Araki et al., 2013).
(C) Transplantation of in vitro iPSC derivatives into the subcapsular renal space of syngeneic mice was tolerated by the immune system, leading to the conclusion that in vitro iPSC-differentiated cells are not immunogenic in autologous recipients (Guha et al., 2013).
(D) Humanized mice displayed different immune responses to autologous iPSC progeny obtained through in vitro differentiation and transplanted into clinically relevant sites. These findings suggest that the expression of immunogenic antigens in in vitro iPSC derivatives depends on the maturity level of the cell type obtained with a specific differentiation protocol (Zhao et al., 2015).

Surprisingly, those authors briefly stated in their discussion that cardiomyocytes obtained through in vitro iPSC differentiation generated a significant T immune response after transplantation into syngeneic mice. These apparently contradictory results suggest that the immune reaction mounted against in vitro iPSC-differentiated cardiomyocytes results from an incomplete or abnormal differentiation process that is not observed when the iPSCs are terminally differentiated and matured through in vivo chimera formation. Similar findings have been described in ESCs. Indeed, in vitro ESC differentiation has been shown to induce aberrant antigen expression in ESC derivatives, which, in turn, elicits immunogenicity (Tang and Drukker, 2011).

Because in vitro iPSC-differentiated cells will likely serve as the main source of cells for therapeutic applications, Guha et al. (2013) specifically evaluated the immunogenicity of in vitro iPSC-derived cells after transplantation into syngeneic mouse recipients. To this end, iPSCs were first differentiated in vitro into one representative cell type of each embryonic germ layer and then transplanted into the kidney capsule of isogenic mice (Figure 1C). An immune response was not observed, thus leading to the conclusion that autologous iPSC-differentiated cells are not immunogenic in autologous recipients. However, an important caveat when interpreting these results is that the ectopic transplantation site does not reflect the actual clinical scenario. Furthermore, the findings of Guha et al. (2013) do not correlate with the immune response observed with the in vitro iPSC-derived cardiomyocytes described by Araki et al. (2013), which were also ectopically transplanted. These opposite results suggest that the immunogenicity of iPSC-derived cells might depend on the final cell type, the similarity of the in vitro-differentiated cells to their in vivo counterparts, including maturation status, or the reprogramming quality of the initial iPSCs. Interestingly, one study compared the immune response to endothelial cells obtained from in vitro-differentiated iPSCs with endothelial cells isolated from in vivo murine aortas (de Almeida et al., 2014). The authors' results pointed to in vitro iPSC-derived endothelial cells and in vivo-isolated endothelial cells as being similarly tolerated by isogenic hosts. The authors concluded that the differences in antigen expression between the iPSC progeny and their in vivo equivalent cells were not sufficient to trigger an immune response after transplantation. However, a gene expression comparison between iPSC-derived and in vivo-isolated endothelial cells was not shown. Thus, the degree of transcriptional divergence the immune system can tolerate because of reprogramming infidelity, genomic instability, or suboptimal differentiation remains unknown. Recently, the immunogenicity of human iPSC-derived cells was investigated using a humanized mouse model with a reconstituted human immune system. Zhao et al. (2015) showed that human iPSC-derived smooth muscle cells were immunogenic, but retinal pigment epithelial cells were not, after transplantation into the skeletal muscle and the eye, respectively (Figure 1D). The authors claimed that the expression of some immunogenic antigens detected in the iPSC-derived smooth muscle cells, but not in the retinal pigment epithelial cells, was responsible for the immune response. Again, the aberrant antigen expression in the smooth muscle cells may result from a suboptimal differentiation protocol or incomplete iPSC reprogramming, which induces abnormal gene expression upon cellular differentiation into smooth muscle cells. Overall, the immune response to iPSC progeny still requires more thorough investigation, specifically regarding the type and amount of gene expression differences between iPSC-derived somatic cells and their in vivo counterparts that can be tolerated by the immune system after transplantation into clinically relevant sites. Finally, future studies should evaluate the immune tolerance to the progeny of genetically corrected iPSCs because the immune system might not show tolerance to the wild-type gene to which it had never been exposed (Wood et al., 2016).

Genomic Stability of hiPSCs

The probability that genomic mutations occur during the reprogramming process has raised concerns about the tumorigenic potential of iPSCs, bringing into question the safety of iPSCs for

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