The future application of induced pluripotent stem cells in vascular regenerative medicine

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This editorial refers to ‘Functional vascular smooth muscle cells derived from human induced pluripotent stem cells via mesenchymal stem cell intermediates’ by V.K. Bajpai et al., pp. 391–400, this issue.

The transplantation of autologous stem cells is the gold standard for regenerative therapy, which includes both local transplantation of the cells to injured organs and the engineering of organs. The use of smooth muscle cells (SMCs) has been shown to improve cardiac, vascular, and respiratory function. SMCs in the vasculature mimic natural healing mechanisms. The important cells for vascular regenerative medicine are mesenchymal stromal cells. The sources of mesenchymal stem cells (MSCs) are well defined and include bone marrow, fat, amniotic fluid, umbilical cord, muscle-derived stem cells, and hair follicle-derived MSCs. The major problem with regenerative therapy remains the source of the cells. MSCs have limited proliferative potential that decreases with increasing donor age. Thus, finding new types of cells remains an important problem. Human induced pluripotent stem cells (iPSCs) are an interesting alternative to MSCs and embryonic stem cells. The iPSCs described in 2006 were of interest because they were collected from adult somatic cells and transformed into stem cells by the ectopic expression of factors, including Oct3/4, Sox2, and c-Myc. The cells have great differentiation potential, similar to embryonic stem cells, as shown by a number of rigorous tests. This technique, pioneered and described by Takahashi and Yamanaka, opened up new possibilities for the application of stem cells in the treatment of many diseases because there are no problems with the availability of somatic cells. Also, the use of autologous cells minimizes transplantation and ethical problems.

Different strategies have been used to make functional, contractile SMCs, but iPSCs have not previously been used for regenerative therapy in vascular medicine. Some studies were designed for proof of concept of the differentiation of human iPSCs to SMCs, but not their use in regenerative medicine. In the current issue of Cardiovascular Research Bajpai et al. publish results of the first trial of differentiation of iPSC into functional SMCs with the aim of using them in regenerative medicine.

The work provides new strategies for differentiating human iPSCs into functional SMCs using an additional step in the differentiation process. In this intermediate step, the cells exhibit characteristics of MSCs. This technique allows for additional expansion of an intermediate cell population before inducing the terminal differentiation of cells in to functionally contractile SMCs. In general, MSCs become senescent after 10 passages. Using the intermediate step, the cells can be propagated 40 times with much higher potential than MSCs. This potential raises a question of what the difference is between human iPSC-MSCs and MSCs. The concept was confirmed for two separate cell lines derived from foreskin fibroblasts and hair follicle-derived MSCs. In addition, the intermediate cells could differentiate into bone and cartilage lineages. However, whether higher levels of cell cycle-promoting genes and the intermediate MSC stage are necessary for human iPSC differentiation into contractile SMCs is unclear. The differentiation of stem cells into SMCs was proved by step decreases in stem cell markers and increased SMC-related genes, including αSMA, CNN1, CALD1, and MYH1. The concept was also confirmed using the tissue skeleton as scaffolding for primitive vascular constructs. Thus, a new application of human iPSCs in vascular medicine was demonstrated. The main achievement relates to a new source of contractile SMCs and a new, efficient strategy of differentiation of iPSCs that can be used for vascular regenerative medicine. This source is easy to obtain and to expand. However, additional research needs to address questions related to the general application of reprogrammed stem cells and how to use iPSC-derived MSCs for this purpose.

Using SMCs obtained from iPSCs in the way described by Bajpai et al. may pose significant risks that could limit their use in humans. The risk is related directly to iPSCs and depends on the methods used for reprogramming adult cells to obtain iPSCs. The technique used for cell transformation includes the integration of transcription factors in the genomic DNA. This procedure increases the oncogenic transformation potential of transplanted cells and tumour development because the factors used for reprogramming are potential oncogenes. Risk can be dependent on cell selection, as different types of cells have variable potential to develop teratomas. The technique of cellular reprogramming...
also uses different groups of oncogenes and different delivery methods. The oncogene groups include combinations of Oct4, Sox2, Klf4, c-Myc, Nanog, and Lin2. The delivery methods use retroviruses and lentiviruses. Of course, other strategies are available to obtain human iPSCs from somatic cells by chemical reprogramming, but these strategies are not as efficient at obtaining human iPSCs and reprogramming. Moreover, reprogramming stromal cells has limited potential, together with a low proliferative capacity of ~1%. Therefore, more work is needed in terms of culturing conditions and the identification and characterization of SMCs derived from iPSCs. These procedures also raise ethical questions, such as the potential use of human iPSCs in the formation of human embryos.

Another important issue is the ease of use of techniques for the analysis of long-term results. The application of human iPSCs requires solution if the cells are to be differentiated in vitro or in vivo. Standardized techniques must be developed to characterize iPSCs and differentiated cells. This work presented in the current issue of Cardiovascular Research has shown proof of concept and demonstrated a general principle, but it is far too inefficient for routine clinical application. Notably, more advanced research on functional cardiomyocytes has shown that variation exists in the expression of genetic markers in the iPSC-derived cardiomyocytes compared with ESC-derived cardiac cells. The maturation process of iPSC-derived cardiac cells is also delayed compared with that of ESC-derived cells. Thus, we can suspect that this situation is related also to SMCs obtained from iPSCs in the way presented in the current work. Additional research is needed to establish the importance of these findings and relate them to specific diseases and applications. Further iPSC basic research will be needed in parallel with the development of vascular disease models.

In summary, the recent work builds new strategies for the use of iPSCs to obtain SMCs through an intermediate population of clonogenic and multipotent MSCs. The advantage of the technique is a high yield of MSCs and SMCs for regenerative medicine. However, iPSC-derived SMCs to be used for therapy will require extensive characterization both in vitro and in vivo relative to what is sufficient to support disease-modelling studies.

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References