The key key to open the door of iPSCs clinical therapy for patients

The discovery of iPSCs is probably one of the most astonishing accomplishments in the beginning of 21st century. This is by 4 early protein factors, the differentiated cells--such as fibroblasts, T and B cells—can return to pluripotent stem cells. This discovery not only laid the foundation for the research field of reprogramming, but also provided priceless sources for stem cell transplantation. Moreover, iPSCs circumvent the ethical concerns by avoiding the use of early embryos. However, could iPSCs eventually be adapted into clinical therapy? It is well known that pluripotent stem cells, including embryonic stem cells (ESCs) and iPSCs can give rise to tumors and also result in immune rejection based on the research using immunodeficient mouse models. Due to the lack of normal immune system of the recipient mice, it is uncertain whether tumor-formation and immune-rejection resulted from the mice themselves or the donor stem cells. To overcome this confusion, we designed a new mouse model by combining the theory of somatic animal cloning, tetraploid complementation, ESCs and iPSCs (Figure).

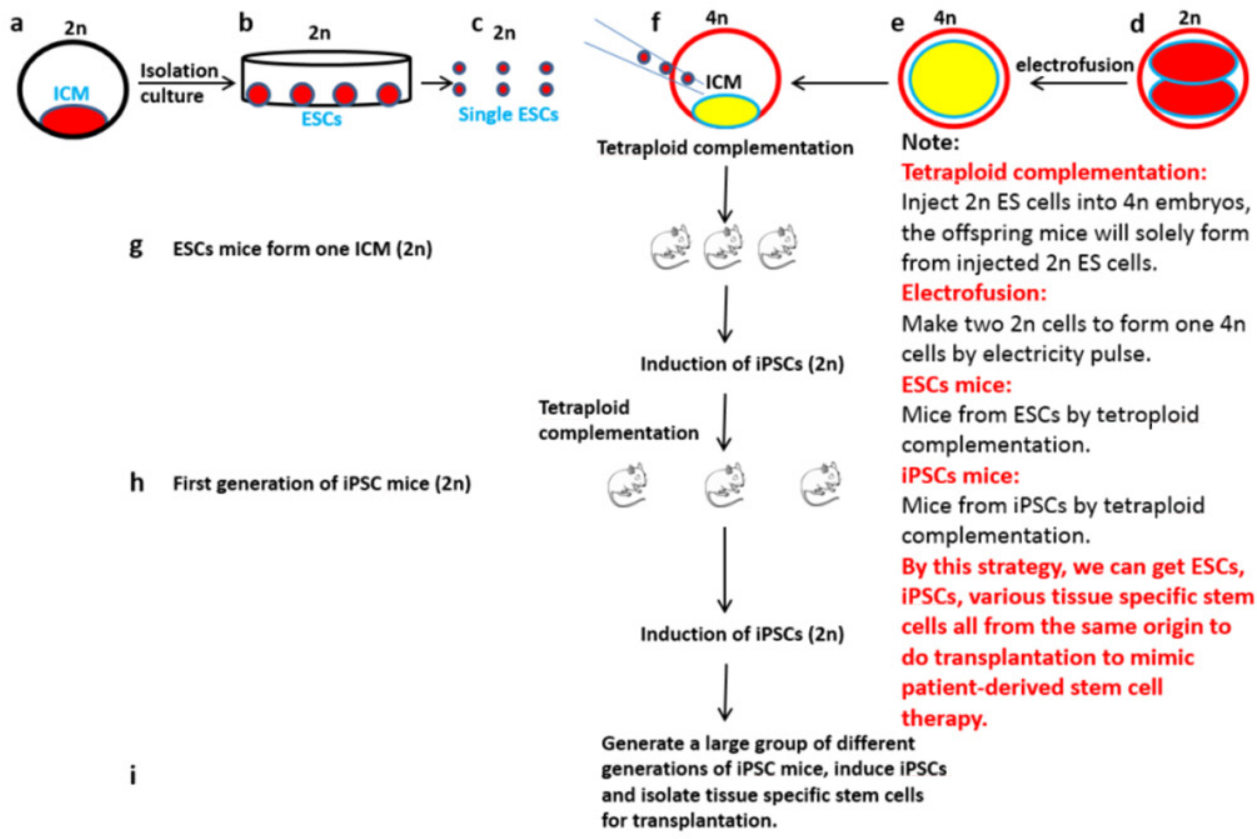

Fig. 1.

There are several advantages to this model. First of all, all the mice cloned from one inner cell mass would be genetically identical. Secondly, via tetraploid complementation, which involves microinjection of the ESCs with two times chromosomes (2n) into early embryos with four times chromosomes (4n blastocysts), the resulted mice would all come from the 2n ESCs. This method grants us the ability to generate a grand population of cloned mice, and each of them would be originated from the same and sole inner cell mass of the blastocyst. When we use these mice as donors for iPSCs, they would be the same with the original donor ESCs. As a result, we can theoretically perform stem cell transplantation between iPSCs, and these mice could mimic the transplantation of iPSCs from the patients into themselves. Because the mice used in this strategy had normal immune system (as contrast with immune-deficient mice), in theory, we can avoid tumor formation and immune-rejection during stem cell therapy. Ideally, the application of iPSCs for transplantation therapy should have full capability to form all tissues. This is of the uttermost importance of ESCs and iPSCs. In addition, the iPSCs and their derivative tissue-specific stem cells should not form tumor. Compared with current mouse models for stem cell transplantation, our “Mouse Clone Model” has several advantages. Firstly, we can test immuno-rejection of iPSCs and various tissue specific stem cells, and to select suitable stem cell lines for transplantation. Secondly, we can assess the tumor formation of iPSCs and other stem cell lines and select suitable stem cells for therapy. Furthermore, after the selection of applicable stem cells, we can investigate the appropriate stages of different stem cells for transplantation. Lastly, this model grants us the ability to decipher the mechanisms of immune rejection and tumor formation with more precision. Because the stem cells and the mouse clones are biologically “selves”, this model provides stronger and more direct evidences for stem cell therapy. This gives further insights for patient-specific iPSCs-based clinical therapy. We suggest the stem cell researchers all over the world to investigate the applicability of iPSCs and tissue specific stem cells for therapeutic applications and take advantage of this model.

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