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EDITORIAL

Towards the safer clinical translation of human induced pluripotent stem cell–derived cells to regenerative medicine

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The development of induced pluripotent stem cell technology would change the paradigm of regenerative medicine using cell or organ transplantation for various kinds of inherited and acquired disorders. In a phase 1 clinical trial (RIKEN) for the treatment of age-related macular degeneration, an autologous human induced pluripotent stem cell (hiPSC)-derived retinal pigmented epithelium sheet was transplanted safely into a Japanese woman in her 70s on 12 September 2014 in Japan. A second transplantation, however, was cancelled because genetic mutations were found in the candidate's hiPSC-derived cells. The investigators revised their protocol of using an autologous hiPSC-derived retinal pigmented epithelium sheet to using an allogeneic one in their next clinical trial to increase the safety of their retinal pigmented epithelium sheet and reduce the risk of tumorigenicity.[1] Although genetic changes do not necessarily cause malignant tumor from hiPSC-derived cells, it is desirable to develop a method which enables us to prepare the transplantable hiPSC-derived cells without oncogenicity. A set of international guidelines for producing clinical-grade hiPSCs as well as their differentiated progeny cells is urgently needed.

Several methods have been reported that may increase the safety and eventually the efficacy of iPSC-based regenerative medicine. The first safety approach eliminates potential oncogenic factors, such as the expression of oncogene c-myc, or integrates the reprogramming transgenes into chromosomes. The latter would be eliminated by using so-called nonintegrating viral vectors. The second safety approach is based on the isolation of desired differentiated cells from other cell types and undifferentiated human pluripotent stem cells (hPSCs), such as the removal of the residual pluripotent cells using fluoresecent activated cell sorting or magnetic beads coated with antibodies against a particular antigen, including SSEA-5 and Claudin-6, and fucose-specific lectin UEA (*Ulex europaeus* agglutinin)-I. The third safety approach entails the direct targeting and killing of oncogenic cells by using cytotoxic antibody recognizing podocalyxin-like protein-1, a chemical inhibitor of stearoyl-coA desaturase, specific monoclonal antibodies, DNA topoisomerase II inhibitor, and suicide gene therapy under transcriptional control of a pluripotency-related promoter. Although each method has a unique advantage, further preclinical and clinical investigations are required before clinical application.[2]

Recently, Kosai's group proposed a fourth safety approach: specific killing of tumorigenic undifferentiated hPSCs using a different methodology. Namely, they demonstrated that conditionally replicating adenoviruses that specifically target cancers using multiple factors (m-CRAs), originally developed as anticancer drugs, may also be useful as novel antitumorigenic agents in hPSC-based therapy. The *survivin* promoter was more active in undifferentiated hPSCs than the *telomerase reverse transcriptase (TERT)* promoter, and both promoters were minimally active in differentiated normal cells. *Survivin*-responsive m-CRA (Surv.m-CRA) killed undifferentiated hPSCs more efficiently than *TERT*-responsive m-CRAs (Tert.m-CRA); both m-CRAs exhibited efficient viral replication and cytotoxicity in undifferentiated hPSCs, but not in co-cultured differentiated normal cells. Preinfection of hPSCs with Surv.m-CRA or Tert.m-CRA abolished *in vivo* teratoma formation in a dose-dependent manner following hPSC implantation into mice. The authors concluded that m-CRAs, particularly Surv.m-CRAs, are novel antitumorigenic agents that could facilitate safe clinical applications for hPSC-based regenerative medicine. They have a plan to start first-in-human clinical trials in human cancer patients in Japan using Surv.m-CRA.[3]

Although the clinical usefulness of these candidate reagents involving Surv.m-CRA technology should be clarified further in clinical trials, one or a combination of the above several reagents would facilitate the clinical translation of hiPSC-derived differentiated cells to clinical regenerative medicine safely and effectively.

Kenzaburo Tani[1,2]
[1]Project Division of ALA Advanced Medical Research, Advanced Medical Science of Internal Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [2]Division of Molecular and Clinical Genetics, Medical Institute of Bioregulation, Kyushu University. Correspondence: K Tani (k-tani@ims.u-tokyo.ac.jp)

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