Cloning and expansion of antigen specific T cells using the iPSC technology: A novel strategy for cancer immunotherapy

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Whereas cytotoxic T lymphocytes (CTLs) represent the most promising therapeutic avenue in cancer immunotherapy, researchers and clinicians have been facing a major obstacle in getting enough antigen-specific CTLs; they easily become exhausted or die during cultivation. To address this issue, we came to the idea of utilizing iPSC technology. When iPSCs are established from antigen-specific T cells, they should inherit rearranged TCR genes, and thus all regenerated T cells should express the same TCR. Since iPSC expansion in vitro is almost unlimited, it should be possible to obtain as many fresh CTLs as needed. In keeping with this idea, we have recently succeeded in regenerating MART1-specific CTLs originally derived from CTLs of a melanoma patient (Cell Stem Cell, 2013). We are also applying this method to the allogeneic transplantation settings, in which the T-iPSCs from healthy donors are banked and the regenerated T cells are given to other HLA-matched patients. In this context, we have succeeded in establishing iPSCs from CTLs specific for WT1 antigen from healthy volunteers. We furthermore have succeeded in regenerating CD8 T cells expressing CD8 alpha-beta heterodimers, which exhibited very high antigen specific killing activity comparable to the original CTLs, and were able to prolong survival of mice bearing WT1-expressing leukemic cells. These results provide a convincing rationale for application of this strategy in clinical settings.