The generation of T cells from iPSCs for immunotherapy

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Abstract

Our laboratory conducts research aimed at realizing immune regenerative therapy by harnessing the properties of iPS cells. One of the immune cells, the T lymphocyte, recognizes target cells antigen-specifically and exhibits its function. The T cell receptor (TCR) required for T lymphocytes to recognize target antigens is formed through gene rearrangement involving genome editing. Therefore, T-iPS cells, which are iPS cells reprogrammed from T lymphocytes, retain the original TCR gene sequence of the parent T lymphocyte. We have utilized this characteristic to establish a method for redifferentiating rejuvenated, antigen-specific T cells from human antigen-specific T-iPS cells in large quantities (Nishimura et al., Cell Stem Cell, 2013; Ito et al., Communications Biology, 2021).

Our lab continues basic research to bring this technology to the clinical stage and has demonstrated the possibility of producing antigen-specific T lymphocytes that can be used for multiple patients by introducing disease-specific TCR genes into iPS cells derived from HLA homozygous donors provided by our institute (Minagawa et al., Cell Stem Cell, 2018). Additionally, we have refined the process of inducing these antigen-specific T cells to use a manufacturing and expansion process that excludes animal-derived components, and by combining it with the introduction of chimeric antigen receptor (CAR) genes, we have demonstrated the potential to supply iPS cell-derived CAR-T lymphocytes to multiple patients (Iriguchi, Yasui, and Kawai et al., Nature Communications, 2021; Kawai et al., Molecular Therapy, 2021; Ueda et al., Nature Biomedical Engineering, 2022). Furthermore, by reducing the immunogenicity of iPS cells using various methods, we have shown the potential to supply therapeutic T lymphocytes from a small number of iPS cell types (Xu and Wang et al., Cell Stem Cell, 2019; Wang et al., Nature Biomedical Engineering, 2021). Some of these technologies have been licensed to private companies and are advancing towards clinical development.

Moreover, we are also developing immune regenerative therapies that capitalize on the characteristics of various T lymphocyte subsets (Kitayama et al., Stem Cell Reports, 2016, Yano et al. Cell Stem Cell, 2024) and natural lymphocyte subsets including NK cells (Ueda et al., Stem Cell Reports, 2018; Ueda et al., Cancer Science, 2020), as well as macrophages (Higaki and Hirao, Molecular Therapy, 2018; Iwamoto et al., Molecular Therapy Methods & Clinical Development, 2021) differentiated from iPS cells. Through these studies, we aim to contribute to the realization of regenerative medicine and the improvement of treatment outcomes for cancer, infectious diseases, autoimmune diseases, and transplantation medicine.

In this presentation, I will introduce the development status of iPSC-derived antigen-specific CD8 killer T cells and CD4 regulatory T cells.

References

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