Center for Stem Cell Biology and Regenerative Medicine

Division of Stem Cell Processing
幹細胞プロセシング分野

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Stem cells represent a valuable cell source in the field of regenerative medicine. Hematopoietic stem cells represent a valuable cell source for transplantation medicine, whereas pluripotent stem cells are newly emerging types of stem cells that have been utilized either for basic research or to develop a curative treatment for various diseases. We have been focusing especially on the utilization of induced pluripotent stem cells as a research platform to elucidate the pathophysiology of intractable diseases based on their proper modeling. Our goal is to establish safe and efficacious treatment for patients suffering from various types of incurable diseases.

Establishment of high-throughput screening platform for RAS-associated autoimmune lymphoproliferative syndrome-like disorder (RALD)

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RAS-associated autoimmune lymphoproliferative syndrome-like disorder (RALD) is a rare genetic chronic disorder of the immune system, characterized by persistent monocytosis and is often associated with leukocytosis, lymphoproliferation, and autoimmune phenomena, but how the oncogenic RAS mutations impact non-transformed hematopoietic progenitor cells (HPCs) remains uncertain. We previously generated KRAS mutant ($KRAS^{G13C/WT}$) and wild-type isogenic ($KRAS^{WT/WT}$) human induced pluripotent stem cells (hiPSCs) from the same RALD patients. Compared with $KRAS^{WT/WT}$ hiPSC-derived hematopoietic progenitor cells (hiPSC-HPC), we found that $KRAS^{G13C/WT}$ hiPSC-HPC exhibited obvious aberrant cell-cycle and apoptosis responses, compatible with "dysregulated expansion," demonstrated by molecular and biological assessment. With screening platforms established for therapeutic intervention, selective activity against $KRAS^{G13C/WT}$ hiPSC-HPC expansion in several candidate compounds, most notably in a MEK- and a BCL-2/BCL-xL inhibitor. The combination of these two compounds could selectively inhibit the growth of primary $KRAS^{G13C/WT}$ HPC. Moreover, we used genome-editing technologies to build a screening platform for other KRAS or NRAS mutation types in RALD. Meanwhile, we developed a feeder-free protocol to differentiate hiPSC-HPC. The purity of generated hiPSC-HPC was as high as 90%, and the cell number was ten times that of the previous protocol. Now, we are trying to generate hiPSC-HPC with KRAS or NRAS mutation and establish a high-throughput screening platform for developing ideal treatment strategies for RALD.