Advanced Clinical Research Center

Division of Hematopoietic Disease Control
造血病態制御学分野

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The main purpose of our research is to elucidate the pathogenesis of hematopoietic diseases and to study the development of therapies for these diseases. For those studies for which we have already determined the therapeutic targets, we will steadily advance the development and proceed to the next stage with clinical application. Specifically, this includes the development of therapies for myeloid tumors targeting Immunoglobulin Superfamily Member 8 and NK cell therapy using CD155/CD112, which are immune checkpoint molecules.

Additionally, we are leading a project for whole genome sequencing of more than 1,400 leukemia samples collected from major institutions that treat hematopoietic diseases in Japan, and the analysis of the genome data of these samples will start this year. In this study, we will comprehensively search for abnormalities occurring in non-gene-coding regions of the genome and beyond, with the aim of elucidating previously undiscovered pathological mechanisms. In addition, we aim to identify the genetic predisposition to the development of leukemia.

Furthermore, in order to promote the elucidation of novel pathogenesis, we are developing a platform to advance the subclassification of diseases based on susceptibility using a drug susceptibility screening system and to elucidate the mechanisms of susceptibility pathogenesis by multi-omics analysis.

1. Immunoglobulin superfamily member 8 maintains myeloid leukemia stem cells through inhibition of beta-catenin degradation

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The identification of characteristic differences between cancer stem cells and their normal counterparts remains a key challenge for cancer treatment. Here, we investigated the role of immunoglobulin superfamily member 8 (Igsf8, also known as EWI-2, PGRL, and CD316) on normal and malignant hematopoietic stem cells, mainly using the conditional knockout model. Deletion of Igsf8 did not affect steady state hematopoiesis, but it led to a significant improvement of survival in mouse myeloid leukemia models. Deletion of Igsf8 significantly depletes leukemia stem cells (LSCs) through enhanced apoptosis and beta-catenin

degradation. At a molecular level, we found that activation of beta-catenin in LSCs depends on Igsf8, which promotes the association of FZD4 with its co-receptor LRP6 in the presence of Igsf8. Similarly, IGSF8 inhibition blocks the colony-forming ability of LSCs and improves the survival of recipients in xenograft models of myeloid leukemia. Collectively, these data indicate strong genetic evidence identifying Igsf8 as a key regulator of myeloid leukemia and the possibility that targeting IGSF8 may serve as a new therapeutic approach against myeloid leukemia.

2. An Immune Checkpoint Molecule DNAM-1/CD112 Axis Is a Novel Target of NK-Cell Therapy in Acute Myeloid Leukemia.

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Acute myeloid leukemia (AML) relapse is considered to occur due to escape of tumor cells from anti-tumor immunity and contribution of immune checkpoints CD155/CD112 to AML progression is assumed. However, both the activation receptor DNAM-1 and inhibitory receptor TIGIT present on natural killer (NK) and T cells bind to CD155/CD112. It is unclear how changes in the expression of CD155/CD112 affect tumor immunity. The Raf-MEK-ERK pathway, related to regulation of CD155/CD112 expression, is one of the targets of FLT3 inhibitors. We investigated the effect of FLT3 inhibitors on the expression of CD155/CD112 and its effects on NK and T cell cytotoxicity. CD155/CD112 expression in AML cell lines with or without treatment of the FLT3 inhibitor quizartinib was analyzed. The direct cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC) of NK cells under FLT3 inhibition were determined by luciferase reporter assay. The cytotoxicity of γδ T cells was also analyzed. CD155/CD112 expression was specifically downregulated by the FLT3 inhibitor in FLT3 mutated cell lines. The direct cytotoxicity and ADCC of NK cells were enhanced. However, the cytotoxicity of γδ T cells with decreased TIGIT expression as compared to that of NK cells was not enhanced. Analysis of clinical trials from the database revealed that high CD155/CD112 expression is associated with poor overall survival. The enhanced cytotoxicity of NK cells against the cells that were treated with FLT3 inhibitors suggests that CD155/CD112 are possible target of FLT3 inhibitors in AML. In addition, we tried to generate genetic engineered NK cells with enhanced anti-tumor cytotoxicity. First, we introduced human IL-15 using lentivirus vector into NK-92 cells, NK cell lines derived from human NK cell lymphoma. Although NK-92 cells are cytokine dependent cell lines, the introduction of IL-15 made NK-92 cells proliferative independent of cytokines. This genetic engineered NK cells were supposed to be useful for our future analyses especially in in vivo analyses using patient-derived xenografts (PDX) mouse model. Furthermore, we performed genome editing in NK-92 cells using CRISPR-Cas9 systems. The cytotoxicity of DNAM-1+/TIGIT- NK-92 cells against AML cells with or without FLT3 mutations was enhanced as compared with that of DNAM-1-/TIGIT+ NK-92 cells. These results indicate the usefulness of genome editing of immune check point-related genes in NK cells to enhance their anti-tumor cytotoxicity. We are in the process of genome editing of immune check point-related genes in *induced pluripotent stem* (iPS) cells and differentiation-induction of genome edited iPS cells into NK cells.

3. Reconstitution of circulating mucosal-associated invariant T cells after allogeneic stem cell transplantation; its association with the riboflavin synthetic pathway of gut microbiota in cord blood transplant recipients.

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Mucosal-associated invariant T (MAIT) cells are a type of innate lymphocyte and recognize riboflavin (vitamin B2) synthesis products presented by MHC-related protein 1. We investigated long-term re-

constitution of MAIT cells and its association with chronic graft-versus-host disease (cGVHD) in a cross-sectional cohort of 173 adult patients after allogeneic hematopoietic cell transplantation. According to donor source, the number of MAIT cells significantly correlated with time after cord blood transplantation (CBT) but not with time after bone marrow transplantation or peripheral blood stem cell transplantation.

The number of MAIT cells was significantly lower in patients with cGVHD compared with patients without cGVHD. We also examined the association between MAIT cell reconstitution and gut microbiota as evaluated by 16S ribosomal sequencing of stool samples 1 mo post-CBT in 27 adult patients undergoing CBT. The diversity of gut microbiota was positively correlated with better MAIT cell reconstitution after CBT. Phylogenetic Investigation of Communities by Reconstruction of Unobserved States analysis indicated that amounts of *ribB* and *ribA* genes were significantly higher in the microbiomes of patients with subsequent MAIT cell reconstitution after CBT.

In conclusion, long-term MAIT cell reconstitution is dependent on the type of donor source. Our data also unveiled an important role for the interaction of circulating MAIT cells with gut microbiota in humans.

4. Genetic deletion and pharmacologic inhibition of E3 ubiquitin ligase HOIP impairs the propagation of myeloid leukemia

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We investigated the role of Hoip, a catalytic subunit of linear ubiquitin chain assembly complex (LUBAC), in adult hematopoiesis and myeloid leukemia by using both conditional deletion of Hoip and small-molecule chemical inhibitors of Hoip. Conditional deletion of Hoip led to significantly longer survival and marked depletion of leukemia burden in murine myeloid leukemia models. Nevertheless, a competitive transplantation assay showed the reduction of donor-derived cells in the bone marrow of recipient mice was relatively mild after conditional deletion of Hoip. Although both Hoip-deficient hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs) impaired the maintenance of quiescence, conditional deletion of Hoipinduced apoptosis in LSCs but not HSCs in vivo. Structure-function analysis revealed that LUBAC ligase activity and the interaction of LUBAC subunits were critical for the propagation of leukemia. Hoip regulated oxidative phosphorylation pathway independently of nuclear factor kappa B pathway in leukemia, but not in normal hematopoietic cells. Finally, the administration of thiolutin, which inhibits the catalytic activity of Hoip, improved the survival of recipients in murine myeloid leukemia and suppressed propagation in the patient-derived xenograft model of myeloid leukemia. Collectively, these data indicate that inhibition of LUBAC activity may be a valid therapeutic target for myeloid leukemia.

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