【Grant-in-Aid for Scientific Research (S)】

Designing precision medicine for poor prognosis leukemia

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Purpose and Background of the Research

● **Outline of the Research**

Leukemia is characterized by uncontrolled cell proliferation of immature blood cells. Arresting the development of normal blood cells results in life-threatening risks: tumor formation, immunodeficiency, and lack of normal blood cells. Despite advance in chemotherapy and stem cell transplant in the past decades, the reasons why clinical prognosis differs from patient to patient are not understood. The aim of this project is to propose the best treatment for each patient based on the molecular characteristics of leukemia.

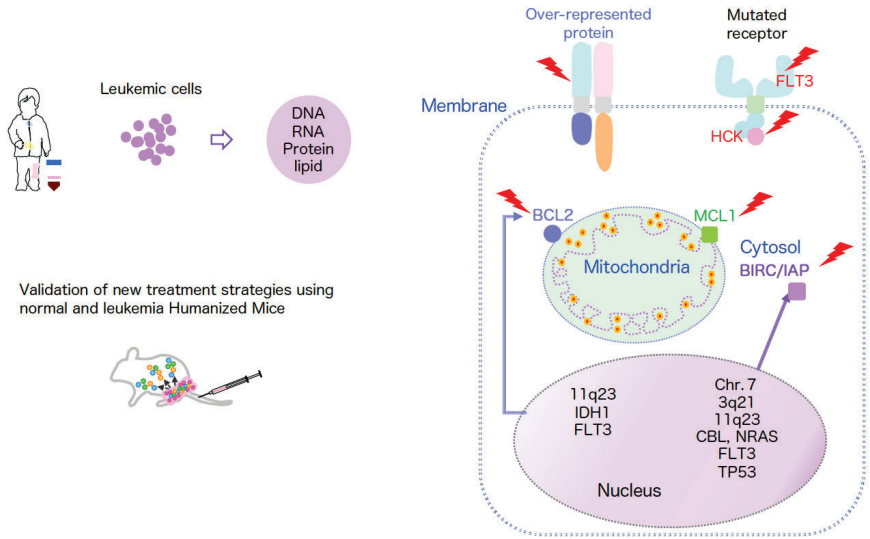


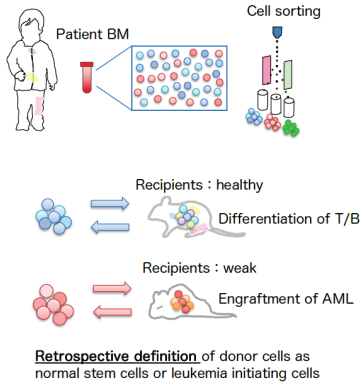
Figure 1. from understanding to targeting poor prognosis leukemia
By understanding what has happened in nuclei of leukemic cells, we aim to understand complexity of the disease. In addition, we integrate biological characteristics with measured omics data. Candidate molecules will be tested using Humanized Mice.

● **Starting research with human samples** Much of medicine and biology has studied normal and diseased systems using mice, extremely good laboratory animals. While mouse research will continue to play a major role in medical and biological research, we further aim to understand human leukemia with diverse genetic and biological complexity, and to find the personalized treatment for this disease. To this end, we will identify therapeutic targets among the which are responsible for the onset or relapse of the leukemia. Using "Humanized Mice," we will validate whether the targets are right and whether the targeted therapies we create will actually work in bone marrow, spleen and liver.

● **Humanized Mice (Mice with normal and diseased human blood/immune systems)**

Using human specimens, it is necessary to validate whether candidate treatment molecules are indeed important in leukemia initiation. In humanized mice reproducing patient leukemia, inhibition of target molecules can affect survival or proliferation of leukemic cells.

Figure 2. Normal and leukemic stem cells that can be transplanted into immunocompromised mice and identified" If lymphocytes develop in the bone marrow and thymus of mice, the cells used for transplantation can be defined in retrospect as normal stem cells. Conversely, if the mice weaken and leukemic cells proliferate, the donor cells are malignant stem cells.



Expected Research Achievements

● **Understanding multiple aspects (gene, biology and metabolites) of leukemia**

1. We aim to find characteristic gene expression patterns in leukemia with mutations in TP53, which occurs not only in leukemia but also in solid tumors. Given the great variety of mutations that occur in TP53, we will evaluate the clinical significance of each mutation and its impact on the course of the disease. To this end, we will evaluate sensitivity and resistance of TP53-mu5q53e leukemic cells to multiple molecular targeting drugs.

2. We will identify proteins expressed on the cell membrane of leukemia, but not expressed by normal blood stem cells and normal cells of other non-hematopoietic organs besides blood. Through engineering of T cells, we take advantage of immunity to suppress activity of the leukemia cells for longterm.

3. In the project, we will establish a quantitative system that measures lipids that leukemia cells utilize for their structure, energy metabolism, and others. Using the system, we will find lipids characteristic of different leukemia subtypes derived from T cells, B cells and myeloid.

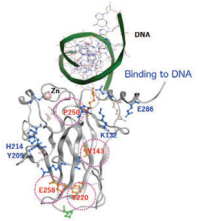


Figure 3. Diverse mutations in TP53

TP53 is a tumor suppressor gene and transcription factor. In its latter function, it binds to the promoter regions of a number of genes to regulate transcription.

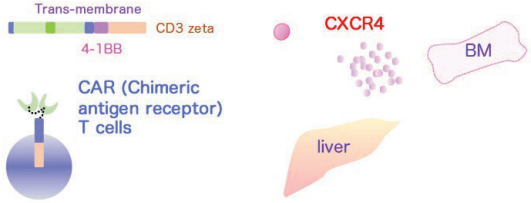


Figure 4. T cell engineering to target leukemia-specific protein on cell surface
It is important to select which of the proteins on the membrane to target in attacking leukemic cells. Throughout engineering, the side effects on normal cells should be carefully considered in order to have strong immune activity. Furthermore, it is necessary to deliver immune cells to deep tissues such as bone marrow and liver precisely and efficiently.

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