Report of the Sysmex Scientific Seminar

the 27th Sysmex Hematology Seminar in Japan

We held the 27th Sysmex Hematology Seminar in Fukuoka city on Saturday, June 5, 2004.
This time, the transmission via satellite was carried out from Fukuoka to the four cities (Sendai, Tokyo, Nagoya, Kobe), so the lecture could be viewed at other places than Fukuoka.

On this day, we were blessed with good weather. There were 1149 participants, Laboratory Medical Technologists, Hematologists, Medical Doctors and many others, who attended the seminar. The seminar focused on Hematopoietic Stem Cell Disorders. The program was as follows.

The 27th Sysmex Hematology Seminar

Date: 5th June, 2004

Place: Fukuoka (Main)
Sendai, Tokyo, Nagoya, Kobe (Satellite)

Lectures:

1. Views on the Pathophysiology and Treatment of Aplastic Anemia
   Seiji KOJIMA
   - Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan.
2. Pathogenesis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as a Preleukemia
   Hideki NAKAMUMA
   - Department of Hematology / Oncology, Wakayama Medical University, Wakayama, Japan.
3. Diagnostic Classification of the Myelodysplastic Syndrome
   Itsuro JINNAI
   - Division of Hematology, Department of Internal Medicine, Saitama Medical School, Saitama, Japan.
4. Self-renewal and Lineage Commitment in Hematopoietic Stem Cell System
   Koichi AKASHI
   - Department of Cancer Immunology and AIDS, Harvard Medical School, Dana-Farber Cancer Institute, Boston, USA.

Chairman:

Masao TOMONAGA
- Department of Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Masami BESSHO
- First Department of Internal Medicine, Saitama Medical School, Saitama, Japan.

Akihisa KANAMARU
- Department of Hematology, Nephrology and Rheumatology, Kinki University School of Medicine, Osaka, Japan.

Views on the Pathophysiology and Treatment of Aplastic Anemia

Seiji KOJIMA

Professor and Chairman of Department of Pediatrics, Nagoya University Graduate School of Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.

.

The combined immunosuppressive therapy (IST) with antithymocyte globulin (ATG), cyclosporine (CyA) with or without granulocyte colony-stimulating factor (G-CSF) is the treatment of choice for young patients with severe aplastic anemia (SAA) who have not HLA-matched family donors during the last decade. Although the combined therapy has produced complete or partial remission in 50 to 70% of patients, long-term survivors are at risk for relapse or secondary clonal diseases such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Several recent studies have suggested that the cumulative incidence of relapse or developing MDS/AML is 30 to 40% or 5 to 15%, respectively.

Allogeneic bone marrow transplantation is another choice for treatment of SAA, The success of bone marrow transplantation is hampered by the high incidence of graft failure and graft-versus host disease (GVHD). The prospective multicenter trial is indispensable for developing optimum conditioning regimen and GVHD prophylaxis for patients with SAA.

Pathogenesis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as a Preleukemia

Hideki NAKAKUMA

Professor and Chairman, Department of Hematology / Oncology, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8510, Japan.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired stem cell disorder that manifests intravascular hemolysis, bone marrow failure, thrombosis, and leukemic conversion. Marrow impairment and leukemia development are more frequent in Japanese patients with PNH than those in Europe and North America. PNH, aplastic anemia, and myelodysplastic syndromes (MDS) are called bone marrow failure syndromes (BFS) that share marrow failure and development of leukemia. Estimated prevalence of patients with PNH is a few per million. There is no significant difference in the prevalence between female and male patients. Age at diagnosis ranges from 10 to 86. Average and medican ages are 45. Japanese patients had a long mean survival time, 32 years. Poor survival was associated with age over 50 years, severe leucopenia at diagnosis, severe infection, and renal failure. White patients died from thrombosis more frequently than Japanese patients, whereas Japanese patients died from bleeding and infection that are ascribable to marrow failure. As one of the alterations in stem cells, the mutations of PIG-A gene was identified. Stem cells that acquired PIG-A mutations do not synthesize glycosylphosphatidylinositol (GPI) , resulting in a deficiency of a series of GPI-linked membrane proteins including complement regulatory membrane proteins such as decay-accelerating factor (DAF) and CD59. Blood cells derived from mutated stem cells share the lack of GPI-linked proteins. Hemolysis and thrombosis are attributable to the membrane defect. In the pathogenesis of bone marrow failure that underlies BFS including PNH, an immune mechanism has been considered to operate. Regarding the mechanism by which PNH clones selectively expand to manifest symptoms, it is suggested that PIG-A mutations confer a relative survival advantage to PNH clones in the setting of bone marrow injury by cytotoxic lymphocytes. Growth phenotype of PNH clones is under intensive characterization. Current report suggests the conditions exist that favor the occurrence of diverse somatic mutations in blood cells, supporting PNH as a preleukemia. Progress in PNH research is leading to a better understanding of pathophysiology of PNH-related diseases such as aplastic anemia, MDS, and leukemia.characterization. Current report suggests the conditions exist that favor the occurrence of diverse somatic mutations in blood cells, supporting PNH as a preleukemia. Progress in PNH research is leading to a better understanding of pathophysiology of PNH-related diseases such as aplastic anemia, MDS, and leukemia.

Diagnostic Classification of the Myelodysplastic Syndrome

Itsuro JINNAI

Professor, Division of Hematology, Department of Internal Medicine, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic disorders and are characterized by hematopoietic insufficiency associated with cytopenia and risk of transformation to acute myeloid leukemia (AML). In 1982 the FAB group made diagnostic criteria for this heterogeneous and incomprehensible group according to a common feature, morphological myelodysplasia. The FAB classification came into wide use and contributed to understanding of MDS. In 2001, a World Health Organization (WHO) has issued a report with proposals for reclassification of MDS regarding morphological approaches. There are three big changes between the FAB classification and the WHO classification:1) The WHO classification has excluded RAEB-T from MDS, and proposed AML to include patients with ≥20% blasts.2) A new category, myelodysplasitic/myeloproliferative diseases, has been proposed for patients with previously had been classified as chronic myelomonocytic leukemia (CMML)3) RA and RARS of the FAB classification have been divided into two categories, respectively. One is unilineage (erythroid) dysplasia for diagnosis of RA and RARS, and the other includes refractory cytopenia with multilineage dysplasia (RCMD). The clinical significance of RCMD is controversial, that is probably due to indistinct criteria for morphological dysplasia. The prognosis of RA patients is usually classified as low risk, but is widely spread. It is important to select high-risk patients from RA (FAB classification). This article reviews the diagnostic process and classification of MDS, and discuss about the minimal morphological diagnostic criteria for MDS especially.

Self-renewal and Lineage Commitment in Hematopoietic Stem Cell System

Koichi AKASHI

Assistant Professor of Department of Cancer Immunology and AIDS, Harvard Medical School, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115, USA.

Over the past four decades, much has been learned regarding the hematopoietic hierarchy that ultimately produces all mature blood cell types from rare hematopoietic stem cells (HSCs). While the existence of lineage-restricted hematopoietic progenitors have been postulated for many years, the ability to prospective isolate HSCs paved the way for the phenotypic discovery of lineage-restricted progenitors downstream of HSCs such as common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs), both of which can be similarly isolated by cell surface characteristics. These progenitor subsets, along with granulocyte/monocyte-restricted progenitors (GMPs) and megakaryocyte/erythrocyte-restricted progenitors (MEPs), appear to represent the major branchpoints at which lineal fate decisions occur. Prospective isolation of each subset permits both global and single cell gene expression profiles to be assayed, from which each of the lineage commitment models can be tested. Transcriptional profiling may also elucidate potential molecular mechanisms of lineage promiscuity and plasticity, which can be tested directly by ectopic activation of specific signaling pathways in purified progenitors to instruct or reprogram specific fate outcomes. In this review, we present a brief history of hematopoietic stem and progenitor cell biology in both mice and humans, with an emphasis on the mechanism of lineage determination.