Int J Hematol
DOI 10.1007/s12185-012-1184-9

Guest editorial: Epigenetics of hematopoiesis and hematological malignancies

Atsushi Iwama

Received: 6 September 2012 / Revised: 12 September 2012 / Accepted: 14 September 2012

Epigenetics refers specifically to the study of heritable changes in gene expression that occur without changes in the DNA sequence. Epigenetic mechanisms confer heritable, but potentially reversible, status of gene activity, mainly through chromatin structure and covalent modifications of DNA and histones. Cellular homeostasis is maintained through epigenetic regulation of gene expression and disruption of such regulation underlies a wide variety of pathological states. Epigenetics is one of the most promising and rapidly growing fields in the post-genome era. Most of the enzymes involved in the covalent modifications of DNA and histones have been identified in the past decade.

Role of epigenetic gene regulation has been extensively analyzed in hematopoiesis, particularly hematopoietic stem cells (HSCs) [1]. An array of genes encoding enzymes for DNA and histone modifications have been characterized, mainly through the study of knockout mice. In contrast, recent genome-wide comprehensive analyses have identified mutations in epigenetic regulator genes in hematological malignancies [2]. Focused on current advances in epigenetics of hematopoiesis and hematological malignancies, the present progress in hematology series reviews the epigenetic mechanisms that maintain the hematopoietic homeostasis and the consequence of epigenetic deregulation caused by somatic gene mutations emerging in hematological malignancies.

Drs. Goro Sashida and I at the Graduate School of Medicine, Chiba University provide an overview of epigenetic regulation of normal hematopoiesis with an emphasis on the role of polycomb-group histone modification complexes and DNA-methylation modulators in HSCs and their progeny. Accumulating evidence suggests that epigenetic machineries regulate growth and differentiation of hematopoietic cells in both a positive and a negative manner. Such bimodal functions of epigenetic machineries fine-tune the hematopoietic homeostasis.

Genetic alterations are not the only causative event in the development of tumors. During tumorigenesis, epigenetic status changes profoundly, as exemplified by the progression of global CpG hypomethylation and appearance of aberrant hypermethylation at the promoters of tumor suppressor genes [3]. Of note, extensive sequencing of cancer genomes revealed that genomic mutations often target genes involved in the epigenetic regulation. Many epigenetic regulator genes appeared to be mutated in hematological malignancies. Dr. Omar Abdel-Wahab at Memorial Sloan-Kettering Cancer Center introduces the latest findings, including his own, on such mutations and describes how these affect epigenetic status and disrupt hematopoietic homeostasis.

Classical leukemic fusion genes derived from chromosomal translocations also target epigenetic regulator genes. Dr. Gang Huang at Cincinnati Children's Hospital Medical Center focuses on such fusion genes. MLL1 is a histone methyltransferase for H3K4. The N-terminal portion of MLL is fused to the C terminus of more than 70 translocation partners. The MLL-fusions activate transcription of target genes by modulating epigenetic status. The recent advances in understanding the epigenetic alterations in MLL-related leukemia have promoted development of inhibitors targeting these epigenetic alterations, providing a promise for the treatment of MLL-fusion leukemia.

A. Iwama (✉)
Department of Cellular and Molecular Medicine,
Graduate School of Medicine, Chiba University,
1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
e-mail: aiwama@faculty.chiba-u.jp

Published online: 27 September 2012

Various types of RNA, such as non-coding RNAs and microRNAs, are involved in epigenetic gene regulation. Alternative splicing is also a form of epigenetic mechanism that enables a single gene to give rise to multiple, differentially spliced versions of a protein, increasing complexity without a change in the genome. Dr. Seishi Ogawa at Graduate School of Medicine, The University of Tokyo, has made the unexpected finding that RNA splicing machineries are major targets for genetic alterations in hematopoietic malignancies such as myelodysplastic syndrome. These findings highlighted the involvement of deregulated alternative splicing in tumorigenesis. He provides the latest information on splicing abnormalities in hematological malignancies.

All of the authors are experts in the epigenetics of hematopoiesis and hematological malignancies, and the reviews include the latest information from these important and exciting areas of research. I hope that readers will find these articles useful and informative.

References

1. Cedar H, Bergman Y. Epigenetics of haematopoietic cell development. Nat Rev Immunol. 2011;11:478–88.
2. Shih AH, Abdel-Wahab O, Patel JP, Levine RL. The role of mutations in epigenetic regulators in myeloid malignancies. Nat Rev Cancer. 2012;12:599–612.
3. Baylin SB, Jones PA. A decade of exploring the cancer epigenome—biological and translational implications. Nat Rev Cancer. 2011;11:726–34.