Guest editorial: Hematopoietic stem cells

Hideaki Nakajima¹

Received: 23 May 2017 / Accepted: 23 May 2017 / Published online: 29 May 2017
© The Japanese Society of Hematology 2017

Hematopoiesis is supported by hematopoietic stem cells (HSCs), a rare population of cells in the bone marrow (BM) specialized to generate all blood lineages throughout lifetime. HSCs retain two important capacities to maintain hematopoiesis—multilineage differentiation and self-renewal capacities. Self-renewal capacity is a common characteristic shared by all somatic stem cells for them not to be depleted by cell division during production of downstream hematopoietic progenitor cells (HPCs). Such HSC capacities are under strict control by various cues from cell interior and surrounding external environment. Molecular mechanism of HSC regulation attracted enormous attention by researchers for decades, and novel technologies such as genetically modified mouse models, highly sensitive metabolome analysis, next-generation sequencing and immunohistochemical analysis of the BM have tremendously moved our understanding of HSCs forward to the current level.

Metabolic pathways are critical targets of HSC regulation, and recent studies have uncovered complex, but fine-tuned mechanism of metabolic regulation in HSCs. Like other somatic stem cells, HSCs are in quiescent, dormant state in HSC niche, a specialized microenvironment in the BM. Oxygen concentration is kept low in HSC niche, particularly in the area away from the marrow vasculature, such as on endosteal surface where many dormant HSCs are shown to reside. In this context, anaerobic glycolysis, rather than oxidative phosphorylation, is preferentially

utilized to supply energy in HSCs. Dr. Takubo was one of the first to show the molecular mechanism for metabolic regulation of HSC under hypoxic state, and he will summarize current understanding of HSC metabolism in view of hypoxia-driven molecular machinery, fatty acid metabolism, amino acid dependence, and nucleic acid-related pathways.

HSC niche is a major source of extracellular factors for HSC regulation and has been under intense investigation for more than a decade. HSC niche supplies a variety of factors maintaining HSC quiescence and their capacities to self-renew and differentiate into multiple lineages, thereby orchestrates proliferation and differentiation of HSCs as well as their progenies. Osteoblasts lining on endosteal surface of the BM was first shown as a major component of HSC niche. However, later studies revealed various cell types including peri-vascular cells, peri-sinusoidal stromal cells [such as CXCL12-abundant reticular (CAR) cells, nestin-expressing stromal cells], peri-arteriolar stromal cells are also critical niche components. Current understanding of HSC niche is summarized in the review by Asada and Frenette, in which they describe a milieu of complex networks constituted by various niche cells in the BM.

External stimuli such as those from infection or inflammations are other sources affecting HSC dynamics. It has been considered that mature immune cells were the ones that sense such external stress and submit signals to hematopoietic stem and progenitor cells (HSPCs) by secreting extracellular factors. However, recent evidence suggests that HSCs and BM microenvironment can also respond to hematopoietic stress signals, thereby modify the status of early hematopoiesis to fit to the external insults. Takizawa and Manz will review the molecular mechanism for HSPCs

✉ Hideaki Nakajima
hnakajim@yokohama-cu.ac.jp

¹ Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan

to respond to and cope with such insults focusing on cytokine networks activated by inflammation and infection.

Finally, recent studies have revealed critical roles of epigenetics such as DNA methylation and histone modification in HSC function and aging. Moreover, disordered epigenetic regulation in HSPCs is tightly associated with malignant transformation of hematopoietic cells, since epigenetic modifiers are recurrently mutated in hematological malignancies. It was recently shown that age-related clonal hematopoiesis or premalignant clonal hematopoiesis [namely, clonal hematopoiesis of indeterminate potential (CHIP)] can be induced by mutation of epigenetic regulators such as DNMT3A or TET2. Recent evidence from large-scale patient studies using next-generation sequencing supports long-standing hypothesis that many of the

hematologic malignancies arise in stepwise fashion by accumulating mutations in HSPCs. Kunimoto and Nakajima are summarizing recent progress in epigenetic regulation of HSCs and how its dysregulation turns HSCs into premalignant state.

I believe this review series will deepen our understanding of HSCs either in normal or malignant state. Like in the past, HSCs will fascinate researchers and be the center of hematological research in the coming decades. The progress in this field will lead to the better understanding of normal and malignant hematopoiesis, and eventually to finding the way to conquer various hematological malignancies.