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Guest editorial: Connecting multiple aspects of hematologic malignancies toward creation of new therapeutics

Fumihiko Ishikawa[1]

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The field of malignant stem cell research was pioneered by acute myeloid leukemia (AML) research. Every hematologist must recall an original article in *Nature*, 1994, in which Dr. Dick and his colleagues found preferential engraftment in immune-compromised mice by $CD34^{+}CD38^{-}$ AML cells [1]. This exciting report on phenotypic and functional heterogeneity within human AML led the way to investigations into potential heterogeneity in solid tumors as well as diverse hematologic malignancies.

The existence of pre-leukemic stem cells is another groundbreaking discovery, reported more recently [2–4]. In the pre-leukemic stem cell model, it is thought that multiple somatic mutations hit immature hematopoietic stem and progenitor cells and incite genetic events that ultimately lead to leukemogenic transformation. Moreover, following the discovery of pre-leukemic stem cells, the presence of AML-associated mutations, such as DNMT3A, TET2, and ASXL1 in the elderly population without hematologic diseases were reported by three groups [5–7]. This phenomenon is thought to be analogous to MGUS in B cell malignancies and was coined clonal hematopoiesis with indeterminate potential (CHIP) [8]. To what extent CHIP contributes to myeloid leukemogenesis is unclear and is an area of active investigation.

One of the most outstanding technical advancements over the past decade is genome sequencing technology enabling investigators to rapidly identify numerous mutations. The discovery of multiple somatic mutations in people with and without diseases has spurred efforts to understand the functional significance of those mutations. Clarifying the roles played by these mutations, individually and in combination, may help create new and effective therapeutic options.

In this chapter, review articles by three experts introduce multiple aspects of hematologic malignancies and how they must be integrated to create novel therapeutics. Cytokine receptor signaling, leukemia-environment interactions, and leukemia stem cell-specific plasma membrane molecules, each essential for understanding biology of leukemogenesis, are presented. Each article clearly discusses the distinction between leukemic stem cells and normal hematopoietic stem cells that contribute to lifelong production and maintenance of homeostasis in blood and immune systems. Furthermore, the merits of both genetically-modified mouse models and patient-derived xenograft models are considered, presenting overlapping and distinct strengths for various research objectives.

I hope that multi-faceted analyses integrating emerging new technologies lead to new pathways to effective treatment options for patients with difficult-to-treat hematologic malignancies.

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✉ Fumihiko Ishikawa
fumihiko.ishikawa@riken.jp

[1] Laboratory for Human Disease Models, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan

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