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Guest editorial: leukemia stem cell

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Leukemia is a clonal, malignant hematological disorder. Recent studies have shown that at least in acute myelogenous leukemia (AML), the clonogenic and leukemogenic activities reside in a minor, primitive fraction of the leukemia cell population. In 1996, Dick et al. showed that the $CD34^{+}CD38^{-}$, but not other fractions of bone marrow cells from AML patients can reconstitute human AML in immunodeficient mice, demonstrating direct evidence for the presence of leukemia stem cells (LSCs). After this finding, the concept of the LSC becomes critical to understand the pathogenesis of leukemia. In this issue, four excellent review articles [1–4] focus on developmental mechanisms of LSCs to discuss how to eradicate them to obtain absolute cure of leukemia.

Cancer should result from the accumulation of multiple genetic abnormalities. In hematopoiesis, the cells accumulating such mutations need to survive for a long time in the human body, and therefore, the main target for mutations should be hematopoietic stem cells (HSCs) that are capable of self-renewal. HSCs harboring multiple mutations can produce a large number of proliferating progenitor populations with identical mutations, which further increases the chance to get another critical hit to transform into LSCs. This outline of leukemia development reasonably fits the concept of blastic crisis from chronic myelogenous leukemia (CML). In CML, a HSC acquires BCR-ABL, resulting in clonal expansion of BCR-ABL-expressing hematopoietic progenitors and mature cells. These HSCs accumulate additional mutations, and their expanding myeloid or lymphoid progenitors finally transform into LSCs of myeloid or lymphoid blastic clones, respectively. In this context, BCR-ABL is an early mutation, and HSCs in CML patients could be regarded as "pre-LSCs". Imatinib mesylate, an inhibitor for kinase activity of BCR-ABL, induces hematological and cytogenetic remissions in nearly every patient in chronic phase of CML, preventing the transformation into blastic crisis, but the cessation of this drug results in relapse of CML in the majority of patients. Therefore, it is important to understand the molecular mechanisms to maintain BCR-ABL-expressing residual HSCs (pre-LSCs) in CML. Ito [1] summarizes key players mediating maintenance of such CML stem cells.

Recent technological advances in genomics have revealed recurrent driver mutations in AML, demonstrating existence of the similar evolutionary processes for LSC development, in which genetic diversity caused by multiple mutations and clonal selection of a population with growth advantage should be critical. In this selection process, it is now clear that pre-LSCs possessing multiple mutations but still retaining ability to differentiate into all mature blood cells progressively become dominant. Chan and Majeti [2] especially focus on mutations related to epigenetic regulation, one of important groups of driver mutations, and summarize the current understanding of their roles in leukemogenesis.

Targeting the LSC should be the ultimate therapeutic strategy to cure leukemias. Xenogeneic transplantation of human cells into immunodeficient mice has enabled to identify cell fractions enriched for LSCs. Ishikawa [3] summarizes the history of xenotransplantation models, and describes his NSG mouse model that is a powerful tool to discover functional properties of LSCs including their cell cycle status and location in the bone marrow. Using the

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similar xenotransplantation system, Kikushige and Miyamoto [4] describe that targeting TIM-3, an LSC-specific molecule, might be a promising approach to selectively eradicate AML clones. Thus, the xenotransplantation system is useful for preclinical trials to obtain "proof-of-concept" for LSC-targeting therapies.

The understanding of LSCs now becomes necessary for every hematologist to pave the way to achieve absolute cure of leukemias. I hope these review articles are useful for readers to understand directions and possibilities of future LSC researches.

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