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COMMENT

Understanding the hematopoietic factory during acute lymphoblastic leukemia

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Initial presentation for children with acute lymphoblastic leukemia (ALL) is often accompanied by abnormalities in peripheral blood counts on routine evaluation of bloodwork. Anemia, thrombocytopenia, and leukopenia or neutropenia are common presenting signs. Indeed, a child who presents with low counts in two cell lines should garner suspicion for a diagnosis of acute leukemia and warrants evaluation by a specialist. These clinical abnormalities hint at a problem in hematopoietic cell function and production of mature blood cells across the three lineages (red cells, white cells, and platelets).

The bone marrow can be considered the production factory for all human blood cells after fetal life, becoming the site for hematopoietic development. With the onset of an acute leukemia, the steady-state production of red cells, white cells, and platelets may be disrupted while the resources and space of the bone marrow are occupied with producing immature leukemic blast cells. In B-cell ALL, these leukemic cells are immature B lymphocyte progenitors. B-cell acute lymphoblastic leukemia is the most common cancer of childhood worldwide with an incidence of 46 cases per 100,000.[1] Interestingly, some children, despite having over 90% leukemia cells in their bone marrow, will still maintain seemingly normal peripheral blood counts and presumably normal bone marrow function. Despite these clinical observations, the frequency and function of residual hematopoietic stem and progenitor cells in a marrow with active leukemia production remain underexplored.

The bone marrow is a complex organ comprised of diverse cell types and specialized niches that together support the development of human blood cells. These specialized niches are important for normal hematopoietic development due to co-localization of specific cells and structures including vasculature, osteoblasts, mesenchymal stem cells, and stromal cells.[2] Further, cellular development in these specialized niches is supported through availability of growth factors, chemokines, and cytokines required for development of a particular cell type and developmental stage.[3] For example, as normal B cells develop in the bone marrow, cell intrinsic and cell extrinsic factors collaborate in successful transition between pro-B and pre-B-cell stages. For instance, just the right amount of IL-7 is important for cells transitioning between pro-B and pre-B cells in the marrow. This is regulated both by the IL-7 producing stroma as well as the level of IL-7 receptor on the developing cells. The local concentration and the gradient of this cytokine dictates transcription factor networks enabling further maturation.[4] Much like a factory, particular cells are produced in specialized areas and the process of lineage development from progenitor to mature cell may occur along a conveyer belt as cells transit their required niches and nutrients along the path to normal development. This tight dance of niche, stroma, local growth factors, and developing cell demonstrates the exquisite regulation of normal hematopoietic development.

How the presence of leukemic cells disrupts this tight regulation has been studied in murine xenotransplantation models or genetic mouse models. Colmone et al., demonstrated that normal $CD34^+$ hematopoietic stem cells preferentially localize in the malignant niche along with ALL cells.[5] This aberrant co-localization results dysfunction in normal hematopoietic production with eventual decline in frequency of HSCs. This decline in both number of hematopoietic stem cells (HSCs) and their output of hematopoietic progeny appeared to be mediated through leukemia cells secreting stem cell factor with local impact on HSCs.[5] More recent studies have further highlighted the numerous ways in which pre-leukemic or leukemic cells may impact the local microenvironment and disrupt the resulting function of normal hematopoiesis. Pre-leukemic cells, those with an initial genetic mutation but not yet fully malignant, have shown upregulation of adhesion proteins or secretion of pro-inflammatory mediators.[6,7] These studies have highlighted the importance of niche, cell adhesion and migration capabilities and secreted factors in enabling leukemia growth, leukemia maintenance and drug resistance in the bone marrow.[8,9] Localized inflammation is emerging as a key factor in both supporting growth of ALL cells while also stifling development of normal hematopoietic cells.[10,11] Many of these studies are completed using cell line models, xenotransplantation into immunodeficient mouse models or genetic murine models, thus not fully representing what may occur in human bone marrow during leukemogenesis.

Demanou-Peylin et al. address this question in their report "*Novel insights into residual hematopoiesis from stem cell populations in pediatric B-acute lymphoblastic leukemia*". Sorting $CD34^+$ $CD38^-$ hematopoietic stem cells from 25 bone marrow specimens in newly diagnosed patients and 5 bone marrow specimens from relapsed patients, the research team performed ex vivo culture or in vivo transplantation experiments to determine the ability of these residual stem cells to produce mature progeny as measured by $CD45^+$ cells. Not surprisingly, the team found variability in the number of HSCs with some patients having fewer than 100 cells while others nearly ten-fold more. Interestingly, they observed that residual HSCs from relapsed patients demonstrated output of

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$CD45^+$ cells more like healthy pediatric HSCs while residual HSCs from marrow at initial diagnosis was significantly stunted. Further, whole transcriptome analysis of $CD19^+$ leukemia blasts demonstrated that transcriptional programs from relapsed samples were more similar to normal $CD19^+$ marrow cells as compared to transcriptional programs at relapse.

With the growth of single-cell, high-parameter technologies, including single-cell sequencing, high dimensional imaging and in situ sequencing, we can expect to learn more about the bone marrow as an organ system and how the various components interact under normal and pathologic conditions. Further, these approaches can enable study of intact human marrow and its diverse cell populations. The healthy bone marrow should be studied across age ranges to understand how the system changes with human development as well as under stressed conditions such as infection, which has been linked to leukemia development.[10] Then, applying similar studies to leukemia bone marrow at diagnosis and again at relapse can uncover derangements in the system under malignant conditions and potentially identify cell populations or regulatory pathways for therapeutic targeting. How the marrow changes and supports leukemia through disease progression from diagnosis to relapse may further refine our mechanistic understanding of data presented by Demanou-Peylin et al. and to the reveal biologic underpinnings of the clinical presentations of acute lymphoblastic leukemia that clinicians regularly encounter.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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