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HEMATOPOIESIS & STEM CELLS

Comment on Choorapoikayil et al, page 184

Pten regulates zebrafish hematopoiesis

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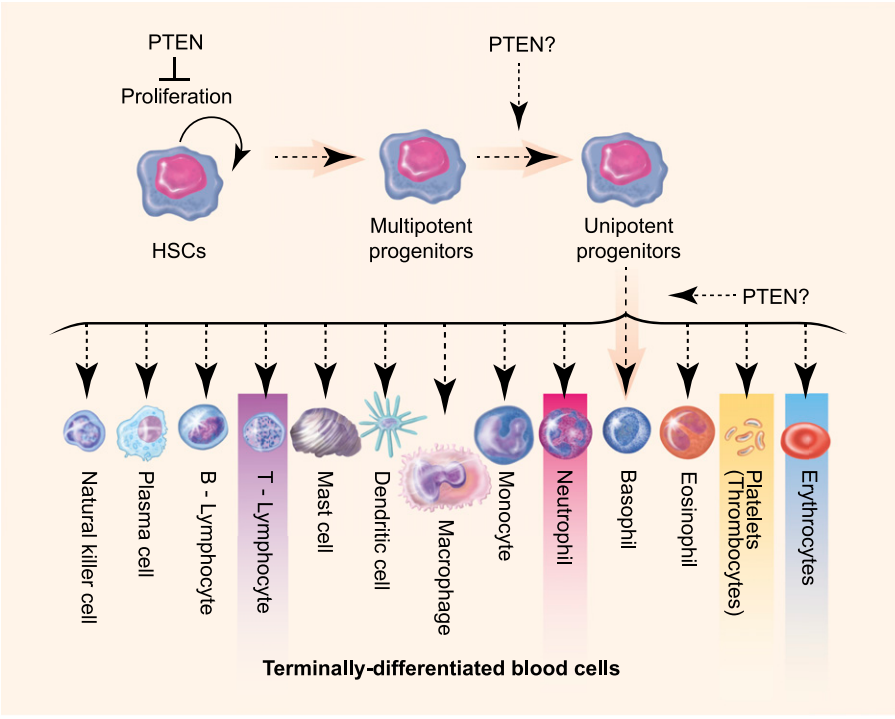
In this issue of *Blood*, Choorapoikayil et al have used phosphatase and tensin homolog (*Pten*)–deficient zebrafish to uncover prominent roles for *Pten* loss in enhancing proliferation of hematopoietic stem cells (HSCs) and eliciting differentiation arrest within lineage-committed blood progenitor cells. These results provide novel insights into the early genetic events that predispose blood cells to malignant transformation.[1]

PTEN is a tumor suppressor gene commonly inactivated in hematopoietic malignancies including T-cell acute lymphoblastic leukemia (T-ALL).[2,3] The early events following *PTEN* inactivation in HSCs and its role in regulating normal blood cell differentiation have not been fully explored.



Multiple roles for PTEN in normal blood cell development. *PTEN* loss would lead to elevated HSC proliferation and to differentiation arrest in lineage-committed progenitor cells. *Pten* loss leads to reduced numbers of mature erythrocytes, thrombocytes, neutrophils, and thymocytes in the zebrafish model (denoted by boxes). Professional illustration by Paulette Dennis.

PTEN is a well-known tumor suppressor that, when lost, leads to constitutive activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway. *Pten* inactivation is embryonic lethal in mice[4] and *Drosophila*[5]; however, conditional loss within HSCs leads to enhanced proliferation and expanded numbers of HSCs.[6,7] Paradoxically, *Pten* loss results in stem cell exhaustion and reduced ability of HSCs to reconstitute the blood system of irradiated mice. Targeted inactivation of *Pten* within the HSC compartment also predisposes mice to developing early onset myeloproliferative disease and T-ALL that are fully transplantable. Together, these observations suggest prominent differences in the role Pten plays in regulating self-renewal of HSCs and leukemia propagating cells derived from committed precursors.[6] To date, it has been difficult to assess how *Pten* loss in HSCs is linked with disease onset later in life and how Pten differentially affects HSCs and committed, lineage-restricted blood cell progenitors.

Choorapoikayil and colleagues report that *Pten* loss leads to enhanced HSC proliferation within the developing zebrafish, but also paradoxically leads to differentiation arrest and expansion of early lineage-committed progenitor cells.[1] *Pten* loss ultimately led to a severe reduction in the numbers of mature thymocytes, thrombocytes, erythrocytes, and neutrophils. Chemical epistasis experiments show that this differentiation arrest can be reversed by LY294002, a potent inhibitor of PI3Ks. Chemical inhibitors restored blood cell maturation even after HSCs colonized and expanded within the caudal hematopoietic tissue, confirming that Pten has important and yet divergent roles within HSCs and early lineage-restricted progenitor cells. These results suggest that *PTEN* loss likely impacts leukemogenesis by blocking cells in early progenitor cell

fates, thereby creating a larger pool of precursor cells in which acquired genetic and/or epigenetic lesions induce frank malignancy.

Given the prominent role PTEN has in expanding the numbers of self-renewing HSCs, it will be important to assess if and how PTEN regulates proliferation in committed, lineage-restricted progenitor cells and leukemia. For example, it is possible that *PTEN* loss both expands lymphoid progenitor cells and increases the overall frequency of self-renewing leukemia propagating cells. Moreover, the downstream pathways mediated by the PTEN/PI3K/AKT signaling axis to ultimately expand progenitor pools, induce malignancy, and maintain leukemic cells has not been fully defined, especially in T-ALL. The PTEN/PI3K/AKT pathway has many downstream effectors including MYC stability to enhance proliferation, activation of the mammalian target of rapamycin (mTOR) pathway to induce dexamethasone resistance in lymphoid malignancies, and suppressed apoptosis through regulation of BAD and NF-κb.[8] Dissecting which of these and other downstream pathways regulate lineage-restricted progenitor cell expansion and leukemic cell maintenance will likely be important for identifying novel therapies for the treatment of a wide range of hematopoietic malignancies. Finally, it will be important to identify the hematopoietic cell stages at which *Pten*-deficient progenitor cells are arrested (see figure), defining whether the PTEN/PI3K/AKT axis exerts differential effects on multipotent or unipotent progenitor cells. The work from Choorapoikayil et al provides critical insights and a relevant zebrafish model to begin to address these important biological and clinical questions.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Rosenberg et al, page 177

Hairy cell: young living longer but not cured

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In this issue of *Blood*, Rosenberg et al provide a detailed retrospective description of the long-term outcome of young patients with a diagnosis of hairy cell leukemia treated with cladribine.[1]

The introduction of the purine nucleoside analogs about a quarter of a century ago dramatically changed the natural history of this once-untreatable chronic leukemia.[2,3] The importance of the current study is that it provides data on a large number of patients under the age of 40 years treated in a fairly uniform fashion at a single institution coupled with careful long-term follow-up. Although the purine analogs can control the disease by achieving complete and durable remissions, the patients are not yet cured. This retrospective study by Rosenberg and colleagues focuses on the clinical characteristics and course of those patients most likely to face the consequences of relapse. Although the statement that the current treatments may provide an opportunity for young patients with this disease to experience "survivals approximating that of healthy individuals,"[1] they will also have to confront the probability of multiple relapses.

The complete remission rate enjoyed by the younger patients was 88% with a median duration of response at 57 months, yet the observation is that the majority of patients will eventually relapse. There is a tremendous range of response duration, from 7 to 246 months. When the therapy was delivered more than 2 decades earlier, immunophenotyping was not routinely included in response determinations. In current therapeutic protocols, immunohistochemical and immunophenotypic analysis are capable of defining minimal residual disease following therapy.

Increasing interest in defining molecular and genotypic biomarkers promises to identify the prognostic subsets with more accuracy. There are new discoveries recently reported regarding the significance of identifying the BRAFV600E mutation in the majority of patients with the classic form of this disease, which has both diagnostic and therapeutic potential for advancement in management.[4] Although the clinical entity of the hairy cell leukemia variant is now distinctly separated from classic hairy cell leukemia by World Health Organization revised criteria, there is increasing evidence that patients with classic hairy cell leukemia who have certain biomarkers (eg, unmutated immunoglobulin gene rearrangement, use of the immunoglobulin gene IGHV4-34, negative marker for the BRAFV600E mutation, or p53 deficit) are likely to have a worse prognosis.[5,6] Other studies have suggested that the extent of minimal residual disease posttherapy may ultimately prove to have prognostic importance, yet some of the patients with minimal residual disease have long-lasting periods not requiring therapy. Although the current study provides substantial evidence for the positive impact of