Scl and stem cell quiescence

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In this issue of Blood, Lacombe and colleagues describe the new discovery that Scl/Tal1 plays a role in the quiescence of HSCs.1 This discovery represents an important advance in our understanding of HSC biology.

The mechanisms underlying maintenance of hematopoietic stem cells (HSCs) remain one of the critical mysteries in blood development. Because of advances in whole genome analysis and in reverse genetic animal model systems, there has been accelerating progress in identification of the genes involved in stem cell self-renewal, lineage commitment and differentiation, and cell-cycle regulation. Critical genes include those encoding hematopoietic transcription factors, cell-signaling molecules, epigenetic modifiers of gene expression, and molecular regulators of cell-cycle progression.2-4 Despite much progress, we still lack an integrated understanding of how these complex genetic networks cooperate to maintain the pool of HSCs or methods to manipulate these processes for therapeutic intent.

One issue of particular importance regards the identification of the mechanisms responsible for stem cell quiescence. At any given point in time, the majority of bone marrow stem cells in mice are in the G0 phase of the cell cycle5 but can be induced to cycle by a variety of stress conditions such as cytotoxic injury6 or hematopoietic stem cell transplantation.7 After hematopoiesis is restored or reconstituted, many of the HSCs return to a quiescent state by mechanisms that are still poorly understood. This regulation of HSC proliferation and pool size is critical for long-term maintenance of hematopoiesis. In this regard, the paper in this issue of Blood by Lacombe et al provides significant new information by demonstrating that Scl/Tal1 is required for maintenance of the quiescent stem cell pool (see figure).

Scl/Tal1 was one of the first hematopoietic transcription factors to be identified and shown to be essential for hematopoiesis through germline deletion experiments in mice.8 However, the role of Scl in adult HSCs is controversial because of potentially conflicting results in conditional Scl deletion models9,10 and because of redundant activities of other related transcription factors.11 The current study shows that relatively high levels of Scl expression specify quiescent HSCs from the adult mouse bone marrow. Functional studies using Scl\(^{+/−}\) bone marrow cells in quantitative transplantation experiments demonstrated that haplodeficient HSCs were significantly compromised in their ability to repopulate myeloid and \(T\)-cell lineages, and that these defects were magnified in secondary transplant recipients. Similar results were obtained using wild-type cells transduced with a shRNA against Scl. Long-term HSCs from Scl\(^{+/−}\) mice showed increased entry into the cell cycle; however, these effects were specific to adult HSCs and not seen in perinatal HSCs up to 4 weeks after birth. The mechanisms for these effects may be explained by the finding that Scl was found to control the expression of

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Sc/I/Tal1 restrains HSC cycling, a duck out of water. Professional illustration by Paulette Dennis.
several important cell-cycle regulators including Cdkn1a and Id1. Consistent with this finding, Id1 deficiency recapitulates many of the HSC abnormalities found in Scl−/− mice.2,13 These results uncover a new and subtle effect of Scl gene dosage/expression on regulating the cell-cycle transitions required for stress conditions that demand high levels of self-renewal, such as limiting dilution transplantation experiments in serial recipients. Given the importance of maintaining HSC reserve for conditions of proliferative demand, these results provide a significant new insight into the role of Scl/Tal1 in hematopoiesis and illustrate the importance of stress models for teasing out elusive phenotypes. It is also noteworthy that relatively modest changes in Scl gene dosage and expression were sufficient for these effects, an observation that is consistent with other known haploinsufficient phenotypes in HSC biology.1,14

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PET positive, PET negative, or PET peeve?

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In this issue of Blood, Horning and colleagues report that there was disagreement by 3 nuclear medicine experts on interpretation of FDG-PET images obtained in the context of a clinical trial in aggressive non-Hodgkin lymphoma 32% of the time.1 These results emphasize the need for standardized criteria to interpret interim PET scans in lymphoma and should cause physicians to question the practice of changing therapy based on PET imaging outside the context of a trial.

Positron emission tomography (PET) is a functional imaging technique that uses a glucose analog (2-fluoro-2-deoxy-D-glucose [FDG]) radiolabeled with the positron emitter fluorine-18 to evaluate glycolytic activity, which is increased in most histologies of lymphoma.2,3 Several studies have suggested a role for FDG-PET in the diagnosis and follow-up of patients with lymphoma, and PET is now recommended as part of routine staging and assessment of response in curable lymphomas—particularly diffuse large B-cell lymphoma and Hodgkin lymphoma.4

More recently, there has been significant interest in performing “interim” PET scans after 2 to 3 cycles of chemotherapy as an early biomarker of resistant disease. A frequently cited trial extolling the benefits of early interim PET enrolled 260 patients with de novo Hodgkin lymphoma and performed a PET scan after 2 cycles of standard ABVD (combination of doxorubicin/bleomycin/vinblastine/dacarbazine) chemotherapy.5 No treatment change was permitted on the basis of the interim PET scan. Two-year progression-free survival for patients with positive interim PET (n = 50) was only 12% and for patients with negative interim PET exceeded 95%. Somewhat lost in these exciting results are details regarding interpretation of the PET scans. Two international expert readers were required to reach consensus for each positive scan. Moreover, lesions with “minimal residual disease,” arbitrarily defined as a standardized uptake value between 2 and 3.5, were considered to be negative prospectively. These criteria have never been evaluated prospectively. Despite these limitations, as a result of this study, cooperative groups in both Europe and the United States are evaluating treatment algorithms that change therapy based on an interim positive PET scan. Many physicians have already adopted this practice. Indeed, a very common question in our consultation clinic is “what to do with an interim positive PET scan?”

For more than a decade, it has been clear that understanding of physiologic uptake and artifacts associated with FDG is critical to accurate interpretation of PET scans.6 False-positive scans can result from brown fat, rebound thymic uptake, and increased diffuse bone marrow and muscle uptake at the completion of therapy, which do not represent refractory disease. Indeed, preliminary results of a trial that incorporated biopsies of PET-positive sites following R-CHOP therapy (rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone) for diffuse large B-cell lymphoma revealed that only a minority of the biopsies (4 of 36) were positive for lymphoma.7

However, for the clinician, binary criteria (positive or negative) are easiest to interpret. Two years ago, consensus criteria were developed for interpreting scans after completion of chemotherapy. Mediastinal blood pool activity was recommended as the reference background activity to define PET positivity in lymphoma, and specific recommendations were provided for interpretation of extranodal sites.8 These international criteria were not...
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