polymorphism did not predict chronicity, but patients with both heterozygous and homozygous variants improved sooner.

Taken together, these clinical and genomic findings could have a significant impact on individualizing the approach to newly diagnosed patients with ITP. While IV Ig administered at diagnosis at a single infusion of 800 mg/kg will not impact development of chronic ITP, the authors report that patients who will eventually enter remission may likely achieve remission sooner if treated with IV Ig. The genotype data provide the first opportunity to use genomics to personalize approach to treatment of childhood ITP. Utilizing these findings, IV Ig treatment could be offered to patients who are most likely to benefit, and those who are not likely to recover as quickly, thus avoiding side effects in those least likely to benefit. If the turnaround time is rapid enough (as is planned in The Netherlands), identifying the variant allele could help to predict the expected disease course of a given patient, an important step toward a more targeted approach to the management of pediatric ITP.

In summary, the TIKI trial is a remarkable large, randomized, prospective study that demonstrates that although IV Ig induces earlier remission, it does not appear to influence development of chronic ITP. As or potentially more important, TIKI confirms an earlier study showing that an FCGR2B polymorphism significantly influences the outcome of pediatric ITP in untreated patients as well as response to IV Ig therapy. Both of these findings are major first steps in individualizing the treatment of children with ITP at diagnosis.

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REFERENCES


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HEMATOPOIESIS AND STEM CELLS

Comment on Hu et al, page 911

Mitochondria confirmed as drivers of HSC fate

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In this issue of Blood, Hu et al elegantly demonstrate that steroid receptor coactivator-3 (SRC-3) is essential for maintenance of hematopoietic stem cell (HSC) homeostasis via repression of mitochondrial biogenesis by acetyltransferase GCN5-mediated posttranslational modification of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α).1

The metabolic phenotype of a cell is emerging as a critical determinant of the fate of stem cells. This is also true for HSCs with a number of players in the metabolic rewiring of HSCs already described.2 Hu et al add a new piece of evidence identifying in SRC-3/GCN5/PGC-1α, a hitherto unappreciated pathway in the maintenance of the HSCs quiescence, which regulates mitochondrial metabolism. SRC-3 is a steroid receptor transcriptional coactivator involved in a number of processes including cell growth and proliferation in normal and cancer cells.3 In particular, SRC-3 has proved to be critical for the maintenance of the cancer stemlike cells and normal hematopoiesis. SRC-3 was found to be highly expressed in murine hematopoietic Lin-Scal1-c-Kit+ (LSK) cells (enriched in HSCs) as compared with lineage-restricted progenitor cells. Hence, Hu et al carried out an extensive characterization of the hematopoietic compartment in SRC-3 knockout mice. Comparing the SRC-3+/− with wild-type (WT) mice, the following was found: (1) increased LSKs and long-term reconstitution HSCs (LT-HSCs), (2) altered cell cycle state in LT-HSCs indicating of reduced quiescence, (3) increased mobilization of LSKs, (4) increased sensitivity of HSCs to cytotoxic stress and irradiation, and (5) reduced reconstitution capacity of HSCs in non-competitive and competitive bone marrow transplantation assays and impairment of in vitro colony-forming capacity. Importantly, bone marrow of lethally irradiated SRC-3+/− mice normally reconstituted WT HSCs showing that SRC-3 intrinsically regulates HSC function.

Next, Hu et al performed a differential microarray gene expression analysis...
identifying upregulation of genes linked to the mitochondrial oxidative phosphorylation (OXPHOS) in SRC-3−/− LSK cells. Thus, in the second part of their study Hu et al validated this observation demonstrating the following in SRC-3−/− HSCs: (1) augmented mitochondrial mass and increased mitochondrial DNA (mtDNA) copy number; (2) enhanced expression of mitochondrial markers; (3) higher mitochondrial membrane potential (ΔΨm), oxygen consumption rates (OCRs), and reactive oxygen species (ROS) generation; and (4) enhanced glucose uptake and adenosine triphosphate (ATP) production (see figure). Altogether, the above observations are consistent with a metabolic rewiring in SRC-3−/− HSCs from an aerobic glycolysis to a mitochondria-driven OXPHOS phenotype.

PGC-1α is a master regulator of mitochondrial biogenesis, and consistent with this notion, Hu et al found enhanced expression of PGC-1α target genes. However, the expression of PGC-1α was unchanged in SRC-3−/− as compared with WT HSCs suggesting alteration at the posttranslational level. Indeed, PGC-1α is known to be regulated by different reversible covalent modification including inhibitory acetylation at a specific lysine residue.

Accordingly, the acetyltransferase GCN5, known to target PGC-1α, was found to be downregulated in SRC-3−/− HSCs, and PGC-1α hypoacetylated. SRC-3 can directly control the expression of GCN5 by specifically binding to its promoter region. Notably, overexpression of GCN5 in SRC-3−/− HSCs (1) enhanced acetylation of PGC-1α, (2) reduced mitochondrial mass and membrane potential, (3) decreased ROS production, and (4) caused recovery of quiescence and long-term repopulating capacity.

Taken together, the findings of Hu et al corroborate the notion that maintenance of HSC quiescence and self-renewal capacity requires suppression of the mitochondrial OXPHOS. This is partly accomplished by the highly hypoxic bone marrow microenvironment where HSCs reside that forces them to rely on a glycolysis-driven low-ROS-producing metabolism. Activation of the mitochondrial oxidative metabolism thus appears to be a prerequisite to the egress of HSCs from their quiescent state, priming them to proliferate and likely making them more responsive to specific differentiation hits.

The novel function of SRC-3 needs now to be integrated with that of other players, such as mTOR, AMPK, and FoxOs, just to name a few, in controlling the balance between quiescent and activated state in the HSC compartment. Notably, all these factors converge, though by different mechanisms, in the control of the mitochondrial biogenesis. Other pathways have been reported to control HSC state/fate by modulating the mitochondrial dynamics (ie, fusion vs fission) and organelle quality control (ie, mitophagy).

In keeping with the multifaceted physiology of mitochondria, what further remains to be established is(are) the mechanism(s) that these amazing organelles put in action in reprogramming the HSCs compartment. In addition to the more efficient bioenergetic capacity of the OXPHOS, needed to cope with
Non-Ph variants in CML: guilty drivers?

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In this issue of Blood, Branford et al report that somatic variants other than BCR-ABL1 are frequently found in patients with newly diagnosed chronic myeloid leukemia (CML). Notably, up to 70% of patients with a poor response to tyrosine kinase inhibitor (TKI) therapy with subsequent blast crisis had clinically relevant genetic variants, including somatic mutations, copy number variations, and novel fusion genes.

CML has been a model used to understand cancer development. Less than 60 years ago, the genetic abnormality, Philadelphia (Ph) translocation (translocation occurring between long arms of chromosomes 9 and 22), was described by Peter Nowell and David Hungerford. Since this discovery, targeted inhibition of the oncogenic BCR-ABL1 tyrosine kinase by small-molecule inhibitors (TKI) has profoundly changed the therapy of CML. Currently, the life expectancy of CML patients is close to that of the age-matched normal population. Further, the current goal of CML therapy is treatment-free remission and discontinuance of TKI therapy without relapse of the disease. However, a small proportion of patients fail to achieve optimal response to TKI therapy; in extreme cases, this will lead to full-blown acute leukemia-like disease with limited treatment options. Although many risk classifications exist (such as Sokal, Euro, and European Treatment and Outcome Study risk scores), chronic-phase CML patients are still treated with “one-size-fits-all” type of therapy starting usually with first-generation TKI imatinib. Interestingly, the disease evolution to blast crisis usually occurs within the first 2 years after diagnosis, suggesting that underlying disease biology in these poorly responding patients is different. If these patients could be identified at diagnosis, alternative treatment that would hopefully avert the subsequent blast crisis could be studied and developed.

To investigate the presence of additional genetic variants, Branford et al sequenced 46 chronic-phase CML patients at diagnosis with whole exome and RNA sequencing. They chose their cohort of patients from 2 extremes: 27 patients with a poor response to TKI therapy with 26 of these evolving to blast crisis, and

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REFERENCES
