foreign physicians, and some changes in the processes of training. But underlying their positive outlook are several trends that bode poorly for one of hematology's most enduring characteristics: its long tradition of "bench-to-bedside" medicine.

The newest of these trends is the mismatch between a growing number of oncology patients and an oncology workforce that not only is too small but also includes more older physicians, who tend to practice less, and a cadre of younger physicians who wish to devote more time to family and lifestyle. This problem is not unique to hematology/oncology. With too few students being educated and too few residents being trained, physician shortages are developing throughout medicine,[1] and there's little relief in sight. The misguided planning efforts of the 1990s ensure that this problem will continue for another decade or more. Faced with this reality, physicians will have to devote more of their total effort to the immediate needs of patients. But if they do, how much time will be left for research, and how much of that research will be laboratory based?

This question also emerges from the analysis of hematology fellowship programs. While pediatric programs, which are characteristically based in academic medical centers, have continued to emphasize research, a very different picture exists on the adult side. Only half of the adult programs are based in academic institutions and most are too small for a vibrant research experience. Indeed, fully half of them offer research for 9 months or less, and most of that research is in the arena of clinical trials. Relatively few fellows appear to be committed to laboratory research. The ASH survey indicates that this number may as few as 30 per year.

Hematology has broadened in scope since I entered it 40 years ago. Combination chemotherapy for childhood acute leukemia, which was being tested then, paved the way for the robust clinical trials enterprise that now exists. But along the way, something happened at the bench. With fewer than 25% of faculty now engaged in laboratory research and with fewer than 10% of their trainees expressing such an interest, the multigenerational phenomenon of bench-to-bedside medicine that spawned many of today's leaders in hematology seems to be on the wane. Even when fellows express an interest, grant support is not readily forthcoming, and even when it is, opportunities to conduct laboratory research are detoured by the demands of patient care. Clearly, there are many factors that make hybrid careers in the lab and at the bedside difficult to pursue. Added to these is the new and powerful trend of inadequate physician supply. Creative responses will be needed if hematology's long tradition of bench-to-bedside medicine is to persist.

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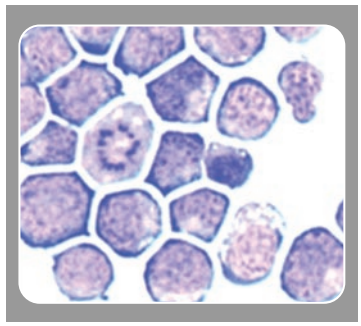
HEMATOPOIESIS

Erythroblast renewal: new roles for RON and Gab1 in EpoR signaling

Hematopoietic stem cells continuously make decisions between self-renewal (proliferation without loss of developmental potential) and commitment/terminal differentiation. At least in leukemia, renewal requires the cooperation of transcriptional regulators/chromatin remodeling factors with signals from cytokine receptors/receptor tyrosine kinases.[1] Recently, we succeeded in expanding primary erythroid progenitors into mass cultures, which requires ligand activation of the erythropoietin receptor (EpoR) and c-Kit together with the glucocorticoid receptor (GR).[2,3] Expansion of erythroid progenitors in vivo during stress erythropoiesis involves the same players.[4] Differentiation of expanded erythroid progenitors to mature, enucleated, and hemoglobinized erythrocytes requires EPO only. Thus, the EpoR can cause both terminal erythroid differentiation and erythroid progenitor proliferation, dependent on cellular context. This is in line with the role of abnormal EpoR signaling, caused by the EpoR mutation R129C or



association with gp55, in its cooperation with the short isoform of RON/Stk in murine Friend erythroleukemia.[5,6] The EpoR is likely to form a signalosome-like complex with several receptor tyrosine kinases (RON/c-Kit) and diverse signal transducers, such as cytoplasmic tyrosine kinases and serine kinases (Janus kinase 2 [Jak2], Lyn, Btk), scaffolding proteins, and downstream adaptor proteins (Gab1/2).[7] It is unclear, however, how the composition and function of this signalosome vary during progenitor renewal and differentiation.

In this issue, van den Akker and colleagues (page 4457) unraveled part of the molecular machinery underlying this dual function of EpoR signaling in erythroblast renewal and terminal differentiation. Using near-primary erythroblasts, they discovered clear differences in EpoR signaling leading to progenitor expansion or terminal differentiation. In particular, they observed a differential role in renewal and differentiation of the tyrosine kinase RON and differential utilization of the scaffolding proteins Gab1 and Gab2 downstream of Ron and the EpoR. Gab1 associates with and is activated in a complex with RON and the EpoR, where Epo signaling activates Ron, which then activates Gab1. In contrast, Gab2 is phosphorylated by the EpoR in a RON-independent fashion using phosphatidylinositol 3-kinase (PI3K)– and Src-family kinase–dependent pathways. Using a Ron-Trk

chimeric receptor driven by a ligand not active on hematopoietic cells (NGF), the authors were able to show that activated Ron fails to activate signal transducer and activator of transcription 5 (Stat5) while inducing signaling via Gab1 as well as mitogen-activated protein kinase (MAPK)– and PI3K/protein B kinase (PI3K/PKB)–dependent pathways. Importantly, RON signaling contributed to erythroblast renewal but failed to drive differentiation, which we previously showed to rely on Stat5 activation.[3]

These findings provide a paradigm for combinatorial action of multiple receptors/signal transducers in the EpoR signalosome, leading to widely different responses in defined progenitors. Similarly, the combined action of receptor tyrosine kinases, in cooperation with transcriptional regulators, may drive hematopoietic stem cell renewal.[1] Thus, the detailed, molecular analysis of signal transduction in near-primary erythroblasts allowing physiologic phenotypic readouts (as presented by van den Akker et al) may well lead to new insights into stem cell function in normal hematopoiesis and leukemia.

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CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Hyper-CVADinib for Ph$^+$ ALL

A little more than 3 years ago, a new drug, then called STI571, burst on to the medical scene, almost overnight establishing a new paradigm for the treatment of chronic myelogenous leukemia. This agent, subsequently named imatinib, proved to be a relatively selective inhibitor of the tyrosine kinase activity of Bcr-Abl. The discovery that most patients with chronic-phase chronic myelogenous leukemia (CML) achieved cytogenetic responses to imatinib was hugely important as a therapeutic advance.[1] Additionally, the finding that inhibiting this one enzyme produced such profound responses confirmed the central importance of Bcr-Abl in producing the malignant phenotype. Not only were responses seen in patients with chronic-phase disease, but (to a lesser degree) patients with accelerated and even blastic-phase disease could achieve transient, clinically important responses.[2] Curiously, in the studies of imatinib to treat blastic CML it was noted that myeloid blast crisis was somewhat more sensitive than lymphoid blast crisis, a surprising result given that, historically, patients with lymphoid disease had a slightly more favorable prognosis.

What then of the other Bcr-Abl leukemia, Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph$^+$ ALL)? This disease has traditionally been notoriously difficult to cure and has typically required the most aggressive available therapy (systemic multi-agent chemotherapy to induce a complete remission [CR] followed by allogeneic stem cell transplantation). In this patient population, imatinib has demonstrable activity, but compared with the chronic phase of CML, the single-agent activity in Ph$^+$ ALL is disappointing, with responses seen in less than a third of patients and time to progression typically only 2 to 3 months.[3]

In this issue, Thomas and colleagues (page 4396) report on treating Ph$^+$ ALL patients with imatinib combined with a standard ALL regimen, hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone). Though the number of patients treated was small (only 11 patients received this as their initial therapy), the comparison to a historic control group treated with hyper-CVAD alone appears promising. The authors treated an additional 9 patients who had previously received hyper-CVAD or other standard induction therapy without imatinib. Five of these patients were in CR when they enrolled in this study, and 4 entered with disease refractory to their initial induction regimen. All 4 patients who failed one cycle of standard induction therapy achieved CR when given combined imatinib–hyper-CVAD therapy.

The results of this trial are encouraging, but they must still be viewed as preliminary. The small number of patients treated, along with the relatively short follow-up (maximum 24 months) and the fact that most (7/11) of the de novo patients underwent stem cell transplantation in first CR, limits our ability to draw definite conclusions about the long-term efficacy of this regimen. Further study of this approach and other combinations of imatinib and chemotherapy will be required to assess the best way to incorporate imatinib into the treatment of patients with Ph$^+$ ALL, and, until greater experience accumulates, it appears premature to abandon the use of allogeneic stem cell transplantation in first CR for these patients.

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