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PREFACE

Hematopoiesis

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In the last two decades there have been tremendous advances in understanding normal hematopoiesis and hematological malignancies at the molecular and cellular level. Although not exhaustive, this issue of *Oncogene* brings together reviews of many of the exciting areas of research in the field.

The first review on the regulation of hematopoietic stem cell (HSC) fate by Krause, focuses on the cellular micro environment that regulates the HSC differentiation state, and on the gene expression patterns that play a role in maintaining a stem cell in its undifferentiated state. The intrinsic mitotic clock of stem cells, which can determine the frequency and number of cell divisions, include telomerase and cyclin dependent kinase inhibitors. Allsopp and Weissman describe the role telomerase may play in the hematopoietic system, the consequences of this with regard to transplantation, and the effect that over-expression of telomerase reverse transcriptase may have on HSCs during transplantation. The ability to increase the stable long-term gene transfer efficiency to primitive repopulating cells in non-human primate models has permitted, for the first time in a large animal model, tracking of individual stem and progenitor cell clones via insertion site analysis. Shi *et al*. describe non-human primate models to study hematopoiesis, and the potential of using autologous transplantation to understand the number of clones contributing to stable hematopoiesis, clonal succession and lineage commitment.

Lotem and Sachs discuss the role of cytokine networks to control the developmental programs in normal hematopoiesis and leukemia. The cytokine cascade that induces growth and then couples proliferation to differentiation, is part of a network of additional cytokines that ensures a balance between inducers and inhibitors of development. Other issues that have clinical relevance are also included, such as how leukemic cells can be reprogrammed, and that there is plasticity in the myeloid differentiation program. The next article, by Zhu and Emerson, describes transcription factors which govern stem cell self-renewal and lineage commitment decisions, and the role of specific cytokines in influencing these decisions. The authors explain how stem cell fate is governed by both intrinsic transcription factors and external signaling pathways initiated by regulatory cytokines.

Several tyrosine kinase proto-oncogenes and their cognate oncogenes associated with hematopoietic neoplasia, including c-*Abl*, *ALK*, c-*Fes*/*Fps*, *Flt3*, c-*Fms*/*CSF-IR*, c-*Kit*, and *PDGFRβ*, are discussed by Scheijen and Griffin. These proto-oncogenes are normally involved in hematopoiesis or hematopoietic cell function. Activated tyrosine kinase oncogenes cause enhanced proliferation and prolonged viability, but usually do not block differentiation; common signaling pathways are involved in mediating these effects. Rane and Reddy describe the intricate relationship between JAKs, STATs and Src kinases in hematopoiesis. They give an overview of JAK and Src kinases, as well as the STAT transcription factors. In addition, how STATs appear to orchestrate the downstream events induced by cytokine/growth factor interactions with their cognate receptors is described, as well as evidence that STAT protein activation is mediated by both JAK and Src family members. The molecular biology of thrombopoietin (TPO) and its cognate receptor Mpl, are described in the article by Kaushansky and Drachman, which also gives an overview of thrombopoiesis, and the signaling by TPO and Mpl. Their article describes the effects of dysregulation of either TPO or Mpl, and the use of TPO as a therapeutic agent.

The molecular mechanisms controlling cell fate decisions are addressed in many of the articles in this issue, and includes lineage specific and general transcription factors, the review by Cantor and Orkin on lineage-specific transcription factors in erythropoiesis, focuses on the participation of these factors in critical protein–protein interactions. Findings demonstrating the functional cross-antagonism between different lineage-specific transcription factors and its implications in leukemogenesis are addressed in this article. Friedman's article on transcriptional regulation of granulocyte and monocyte development reviews the complexities of orchestrating the myeloid developmental program. This includes cooperative gene regulation, synergistic and inhibitory protein : protein interactions, promoter auto regulation and cross-regulation, regula-

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tion of factor levels and induction of cell cycle arrest. Myeloid differentiation primary response (MyD) genes, cloned by virtue of being coordinately induced upon the onset of terminal myeloid differentiation, include transcription factors (*IRF*-1, *egr*-1, *jun*) and, at the time of cloning, novel [*MyD88*, *MyD118* (*Gadd45β*), *MyD116* (*Gadd34*)] genes. The review by Liebermann and Hoffman delineates the role of the different MyD genes in blood cell development, where they function as positive regulators of terminal differentiation, participate in lineage specific blood cell development, and control growth inhibition and apoptosis.

The cell cycle status of hematopoietic cells varies, from extended quiescence to rapid proliferation. Steinman's review focuses on the cell cycle regulators which control stem cell quiescence, progenitor replication and cell cycle exit upon differentiation, and the intersections between the cell cycle and differentiation machinery.

The proto-oncogene c-*myc* participates in hematopoietic homeostasis by regulating proliferation, differentiation and apoptosis, and alterations in its expression are associated with hematological malignancies. The review by Hoffman *et al*. addresses how c-Myc is regulated, the effects of dysregulation of c-Myc on differentiation and survival, and how altered c-Myc function is associated with leukemogenesis.

Cytogenic abnormalities are detected in more than half of newly diagnosed cases of acute myeloid leukemia (AML), where genes encoding transcription factors are usually found at one of the breakpoints. The shared features, both structural and functional, of these leukemia-associated fusion proteins are discussed in the review by Scandura *et al*., suggesting that these 'variations on the theme' underlie the aberrant growth and block in differentiation that is the hallmark of acute leukemia cells. An adjunct and powerful tool to study normal and aberrant hematopoiesis is the mouse model. Manipulation of gene expression *in vivo* in the mouse has advanced tremendously over the last several years. Bernardi *et al* describe recent important technological developments that made it possible to reproduce in the mouse the genetic lesions that characterize human hematological malignancies, providing examples of the advantages and limitations of the various approaches. Included is a discussion of the power of the mouse model to develop and test novel therapeutics in pre-clinical studies.

To ensure hematopoietic homeostasis requires appropriately regulated proliferation, differentiation and programmed cell death. Reed *et al*. provide an overview of apoptosis pathways and genes, and summarize the genetic lesions identified in apoptosis regulatory genes of hematological neoplasms. Also, novel strategies for therapeutic intervention provided by apoptosis targets are discussed. The number of genes with proven or suspected tumor suppressor activity is increasing continuously; many of these genes would promote apoptosis. In addition, tumor suppressor genes could be involved in cell cycle control and terminal differentiation. Krug *et al*. provide an overview of the current knowledge about the involvement of tumor suppressor genes in hematopoietic differentiation and in the formation or progression of hematopoietic malignancies. Aberrant differentiation is often a feature of the malignant phenotype of many acute leukemias and some lymphomas, often resulting from a single genetic alteration. This provides a site-specific target for therapy. Miller and Waxman review the status and the potential for differentiation therapy in the treatment of hematologic malignancies, including a discussion of the effectiveness of differentiation therapy in APL.