Introduction to the Review Series on “Hematopoietic Stem Cells”

Margaret A. Goodell, PhD
Associate Editor, Blood

The continuous regeneration of the blood from elements of the bone marrow has been a source of fascination for scientists and clinicians since the first pathologists gazed down their microscopes upon the beautiful and diverse cell types of the hematopoietic system. While the presence of hematopoietic stem cells (HSCs) were postulated in the 1800s, the development of colony assays and transplantation assays in the 1950s enabled functional definitions to be established, that finally made their activity quantifiable, and their study feasible. Since then, they have continued to be studied intensely.

Over the past fifteen years, a number of technological advances have further accelerated research on the identity of stem cells and their progeny, the intrinsic and extrinsic modes through which they are regulated, and finally, progress has been made toward the long-sought goal of generating HSCs de novo, from embryonic or adult tissues. Here, we present a series of reviews that describes the latest advances in these areas, and highlights some of the new opportunities for progress in the coming decade.

Remarkably, we continue to revise our view of the HSC. Two decades ago, techniques such as retroviral marking allowed HSCs and their progeny to be tracked in vivo. These experiments unequivocally supported the existence of the stem cell, and established our current views of the kinetics and stability with which they contribute to hematopoiesis over time. Now, with new approaches to following HSC activity, using new transplantation and marking strategies, these views are dramatically being revised. An overview of the history and current status of our understanding of HSCs grounded in murine HSC biology is presented by Connie Eaves.

Sound functional definitions of HSCs have allowed enhanced purification of HSC, which in turn facilitates study of intrinsic and extrinsic regulation. The study of the gene networks involved in stem cell decision-making has advanced along with molecular approaches such as gene expression profiling and localization of histones and transcription factors throughout the genome. These approaches are leading to a greatly enhanced understanding of how competing molecular signals are integrated, influencing outcomes in terms of differentiation and self-renewal of HSCs; these advances are reviewed by Berthold Göttgens.

The past decade has also seen an increasing appreciation of the role that the microenvironment, or the niche, plays in regulating HSC function. The development of
mouse lines in which individual lineages of cells in the bone marrow are labeled, as well as advances in imaging technologies, have facilitated new insights into the specific interactions that HSCs enjoy. These insights, reviewed by Philip Boulais and Paul Frenette, will lead to and appreciation of the how the niche influences the response of HSCs to the demands of hematopoiesis, and the contributions the niche makes to pathogenic states.

While great strides have been made in understanding the mechanisms that regulate murine HSCs, the study of human HSCs has lagged behind, in part due to the lack of good models for their study, despite the decades-long use of mouse xenografting to support human hematopoietic cell growth. Better understanding of the immunological barriers to supporting human cells in mice have allowed the development of new mouse models that can now be exploited. These models, and their utilization for the study of normal and malignant hematopoiesis, are reviewed by Susumu Goyama, Mark Wunderlich, and James Mulloy.

Ultimately, hematopoietic transplantation would ideally become independent of large amounts of donor cells. This would be possible if we could generate engraftable stem cells for bone marrow transplantation. Despite early successes in generating small amounts of differentiated blood cells from embryonic stem cells, this goal has proved more challenging than expected for a variety of reasons. As work progressed, induced pluripotent stem cells were discovered, and approaches for directly generating hematopoietic cells from non-pluripotent cell types have emerged. While replacement of donor tissues is still some way off, the advances in de novo generation of hematopoietic cells are transforming our views about HSC identity and development. Linda Vo and George Daley review recent progress in this area.

Together, these expert reviews provide a perspective on the last decade of work in HSC biology, and lay out the directions for future work.

The reviews presented are:

Connie J Eaves

*Hematopoietic Stem Cells: Concepts, Definitions and the New Reality*

Berthold Göttgens

*Regulatory Network Control of Blood Stem Cells*
Philip E. Boulais and Paul S. Frenette

*Making sense of hematopoietic stem cell niches*

Susumu Goyama, Mark Wunderlich, James C. Mulloy*

*Xenograft models for normal and malignant stem cells*

Linda T. Vo and George Q. Daley

*De Novo Generation of HSCs from Somatic and Pluripotent Stem Cell Sources*

We hope you find this review series of interest.

Margaret Goodell

Associate Editor, Blood
Introduction to the Review Series on "Hematopoietic Stem Cells"

Margaret A. Goodell