Book Review

Lymphohematopoiesis in health and disease

Thomas Böhler, Karsten Stahnke and Klaus-Michael Debatin

University Children's Hospital, Ulm, Germany

Hematopoietic Lineages in Health and Disease. Edited by Nydia G. Testa, Brian I. Lord, T. Michael Dexter. Marcel Dekker, Inc., New York, Basel, Hong Kong: 1997. Pp. 384. ISBN: 0-8247-9512-1. US\$150.00.

In the rapidly evolving field of biomedical research in hematology, oncology and immunology with the exponential increase in knowledge every textbook is in danger of being outdated when printed. In their recent publication 'Hematopoietic Lineages in Health and Disease' (Marcel Dekker, Inc., New York, Basel, Hong Kong 1997) Nydia G. Testa, Brian I. Lord and T. Michael Dexter delineate an integrated view of lymphohematopoiesis in human health and different disease states, focusing in particular on the effect of cytokines on cell survival, proliferation, differentiation and function. In order to achieve the difficult task of covering an extremely wide and exponentially growing field of basic, translational and clinical research, the editors deal with the physiology of hematopoietic cells (chapters 1–10) and cover more clinical aspects such as the pathology of leukemogenesis and the therapeutic use of recombinant hematopoietic growth factors (chapters 10–13). In a comprehensive introductory chapter the reader is provided with a brief historical overview on major achievements in mammalian stem cell biology, current nomenclature and the key concepts of self renewal, proliferation and differentiation of stem cells *in vivo*. The current state of knowledge regarding the role of stromal cells and the extracellular matrix in stem cell differentiation in murine and human long-term bone marrow cultures is summarized in chapter 2. Most chapters, however, deal with specific hematopoietic lineages. Chapters 3 and 4 provide an excellent and up-to-date summary of the current knowledge in myelopoiesis, monocytopoiesis and mature neutrophil and monocyte/macrophage function. A detailed description of cellular antigens, receptors, growth factors and transcription factors involved in the myelomonocytic maturation process is provided with a main focus on human myelopoiesis. When discussing the results of animal studies on manipulation of mature phagocytes *in vivo* the authors point to one of the critical problems of translational biomedical research stating that 'study design of most animal experiments has been unimaginative with insufficient attention paid to clinical relevance' (e.g. treatment with growth factors prior to introduction of infection without administration of concurrent specific antimicrobial drugs). Chapter 7 provides an excellent review of both basic and clinical aspects of development and function of eosinophilic granulocytes, which seems to be strictly under control of interleukin (IL)-5 (and eventually additional T-cell-derived signals) and their role in allergic and inflammatory diseases. As in most chapters of this book, data on human experimental models

are always discussed on the background of extensive studies in murine models including gene knock-out or transgenic mice. Unfortunately, chapters on basophilic granulocytes and mast cells (chapter 8), erythropoiesis (chapter 5) and megakaryocytopoiesis (chapter 6), while presenting interesting insights into models of cell development and function, have much more emphasis on murine systems and provide only few data on human studies, making them less valuable for the clinician searching for background information relevant to clinical research. Chapter 9 describes the molecular mechanisms of signal transduction in different hematopoietic lineages in detail. It is a brief and elegant overview on signal transduction from membrane receptors for protein kinases, transcription factors and immediate early gene expression in a comprehensive way that can be used as a reference for terminology and nomenclature throughout the book. Chapter 10 deals with normal lymphopoiesis and leukemogenesis and provides some comprehensive tables that may be useful for a quick overview of T- and B-cell development in mice and humans. Current concepts of leukemogenesis derived from experiments in murine and human cell lines and primary samples from patients with acute lymphocytic leukemia (ALL) are discussed. The diversity of genotypic abnormalities found in ALL, the functional importance of several mutations (leading to a putative selective advantage) in certain differentiation-linked genes and the method of expanding primary ALL-blasts (that are only rarely maintained in *in vitro* culture systems) by injection into severely combined immunodeficient (SCID) mice are described in detail. Molecular mechanisms of leukemogenesis in myeloid and myelo-monocytic lineages are discussed less extensively. Chapter 11 describes clinical studies regarding the use of recombinant hematopoietic growth factors in myelodysplastic syndromes (MDS). Chapter 12 summarizes some interesting data on the expression and function of the c-kit receptor (CD117) and the c-kit ligand (stem cell factor) in human tumor cell lines and primary samples from patients with AML, Burkitt-lymphoma, T-ALL and T-NHL (non-Hodgkin lymphoma) and includes a scrupulous analysis of possible artifacts induced by cryopreservation and *in vitro* culture of primary patient samples, that should be taken into account when extrapolating data from cell lines and cultured patient samples to the *in vivo* situation. Chapter 13 finally covers the important topic of therapeutic modulation of mature cell production. Concise information is given on the pharmacol-

ogy of recombinant human hematopoietic growth factors and useful tables are provided summarizing the effect of therapeutic doses of these factors on the recovery of neutrophilic granulocytes and platelets following cytoreductive chemotherapy as well as different conditioning regimens in bone marrow transplantation and autologous stem cell transplantation.

There are few weaknesses and limitations in the concept of this volume that have to be mentioned. Most importantly, while in most chapters the role of growth factors and signaling pathways in hematopoietic lineage commitment, cellular differentiation, maturation and function is extensively covered, the molecular mechanisms of programmed cell death (apoptosis) are not addressed to the same extent. The concept of apoptosis throughout the book seems to be confined to the 'death by default' model of growth factor withdrawal (i.e. cells that do not receive the appropriate survival signals undergo programmed cell death unless rescued by specific growth factors needed for cellular survival, growth and differentiation). However, apoptosis in hematopoietic cells is also induced by specific receptor-ligand interactions (e.g., CD95/APO-1/Fas). For example, it has been shown that CD34+ human hematopoietic stem cells express CD95 upon activation and that the sensitivity toward CD95-signaling may be important for pathogenesis of severe aplastic anemia. Furthermore, the anti-apoptotic effect of cytokines has been shown to be mediated by Bcl-2 in several hematopoietic cell lines. It would have clearly been of great interest to provide an overview on these new

molecular mechanisms to the reader. In general, authors and editors succeeded in generating one of the first comprehensive textbooks that form a bridge between basic biomedical research and clinical applications. It would be helpful if some of the authors introduced more didactic schemes and tables that could be quickly referred to when reading other chapters. The clinically relevant topics in hematopoiesis that are addressed are somehow limited to oncology (leukemogenesis, chemotherapy, bone marrow and stem cell transplantation) and only spurious information is available on other diseases such as congenital cytopenias (unraveling the molecular mechanisms of their pathogenesis might substitute for the extensive use of mouse models of certain disease states) or acquired diseases such as aplastic anemia or virus-induced cytopenias (e.g. during infection with the human immunodeficiency virus). Interesting aspects of hematopoietic differentiation such as the role of retinoid acid receptors or interferons are only marginally covered. Nevertheless, despite these few shortcomings and limitations the volume might be a useful primer for both clinicians and basic researchers who want to update their knowledge on research advances in hematopoiesis during recent years. Due to the fact that some chapters cite only references up to the year 1994 (others include publications up to 1996), the information should be complemented with actual review articles that appear regularly in major journals. It might as well be a source book for 'cell death professionals' interested in an introduction into philosophy of their 'growth and differentiation counterparts'.