Megakaryocyte Biology and Precursors:

in vitro Cloning and Cellular Properties

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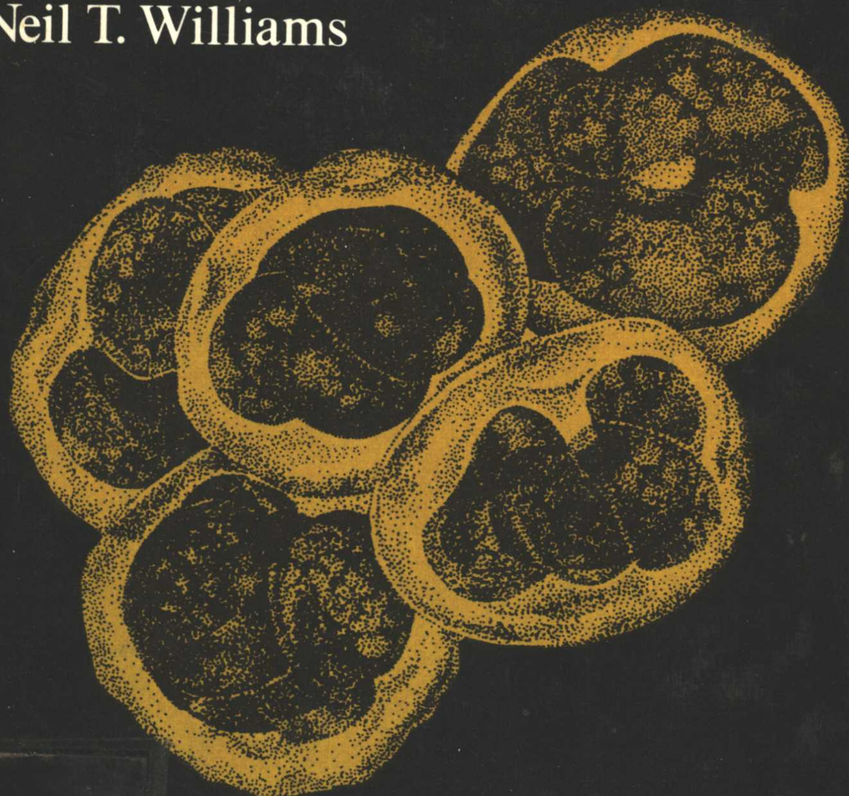

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MEGAKARYOCYTE BIOLOGY AND PRECURSORS: IN VITRO CLONING AND CELLULAR PROPERTIES

Proceedings of the Symposium on Megakaryocytes *In Vitro* held at the Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, Georgia, U.S.A., May 1–2, 1980

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Preface

Megakaryocytes are unique cells. They occur only in mammals and their main function is to produce platelets as first demonstrated by Wright in 1906 (*Boston Med. Surg. J.* 154:643–645). Each one gives rise to a few thousand enucleate platelets by a precisely controlled cytoplasmic division (Behnke, *J. Ultrastr. Res.* 24:412–433, 1968). Megakaryocytes are polyploid, resulting from repeated mitoses without cell divisions (Jolly, *Traité Technique d'hématologie*, Paris: Maloine, 1923). The nature of these mechanisms and their consequences are still poorly understood. The cells are of interest to cell biologists and physiologists for these unusual mechanisms, to hematologists for their involvement in various disease processes, and more recently to experimental pathologists and others for their perspective on platelet contributions to hemostasis and arteriosclerosis.

Study of the biology of megakaryocytes and the regulation of their development from uncommitted stem cells to platelets has been severely limited by the extremely low incidence of megakaryocytes in the bone marrow (0.01–0.3% of all nucleated cells, depending on the age and species). In the last five years, *in vitro* techniques have become available which have permitted megakaryocytes to be isolated in reasonable yields (Levine and Fedorko, *J. Cell Biol.* 69:159–172, 1976) and their precursor cells to be studied and monitored in cloning assays (Metcalf et al., *Proc. Nat. Acad. Sci. USA* 72:1744, 1948, 1975).

This book and the conference from which it was drawn were planned to provide a forum for presentation of new data derived from these *in vitro* techniques. Although specific topics such as morphology, thrombopoietin, etc., have been the subjects of review articles, no single comprehensive source on megakaryocytes has been available. We have brought together in this volume a wide spectrum of information and have included discussions in an attempt to reconcile possible differences of interpretation. More than that, we hoped to provide a synthesis of all that has been

done in this field, to reach a common understanding not only of terms but also some of the mechanisms in which these cells are involved. The *in vitro* work of the last five or six years has been clarified and the remaining problems are better defined. The highlights below illustrate some of the new perspectives achieved, but it is left to the reader to survey the rich complexity contained herein.

In this book, the definitions of stages involved in the maturation sequence have been more clearly described than ever before. Megakaryocytes are found in sizes down to 5 μm in diameter, but are recognized by routine microscopy down to only 10 μm. The smaller cells are detectable by specific markers such as acetylcholinesterase activity in the mouse and rat or fluorescent antibody detection of platelet antigens in the human. These cells were previously thought to be a separate class of progenitors, but with the presence of these biochemical markers they are now thought to be newly differentiated megakaryocytes. Little is known of the length of this stage or of the events which encompass it, but it does appear to be important in ploidy amplification in response to platelet demand.

Several chapters are devoted to data on qualitative or biochemical contributions of megakaryocytes to platelets. It now seems likely that all of the substances found in platelets are synthesized in the megakaryocytes. The one exception is serotonin, for which megakaryocytes have the same uptake capacity as do platelets.

Analysis of megakaryocytes using objective criteria has permitted the conclusion that, contrary to earlier reports, 8N megakaryocytes are the most frequent megakaryocyte class in the bone marrow. Furthermore, it was reported that each *in vitro* colony contained megakaryocytes of different rather than uniform ploidy levels.

Megakaryocytopoiesis appears to be controlled at two levels. A compartment of precursor cells was shown to proliferate in response to various conditioned media, but was not influenced by platelet levels. These pre-megakaryocytes are identifiable only by measuring their progeny, with the above biochemical substances as useful identifying markers. Ploidy amplification in the differentiated megakaryocyte compartment occurs in a positive feedback control mechanism in response to platelet demand and is mediated by thrombopoietin. Thus, separate factors independently influence proliferation and maturation events. It is not known whether only a single factor is involved at each level.

No attempt has been made to recommend particular nomenclature. The authors in this text and elsewhere have used different terms to describe similar factors or cell populations: thrombopoietin, thrombocytopoiesis stimulating factor, or megakaryocyte potentiator; CFU-M or Meg-CFC; and Meg-CSF, Meg-CSA, or MK-CSF.

Many useful observations about the biology and physiology of megakaryocytes have been assembled in this book from *in vitro* studies. It should be stressed, however, that the information gained is meaningful only in an *in vivo* context. For example, following induction of thrombocytopenia in animals, the increase in differentiated megakaryocytes precedes, not follows, the increase in clonable precursor cells (Meg-CFC). Data derived from both these approaches further our understanding of the normal development of megakaryocytes and thus provide a basis for exploring abnormalities in states of perturbed thrombocytopoiesis.

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This volume is the edited proceedings of a symposium entitled "Megakaryocytes *In Vitro*" held in Atlanta on May 1 and 2, 1980. The symposium was sponsored by the Centers for Disease Control and by Hemophilia of Georgia, Inc. The symposium organizing committee was comprised of Drs. Bruce L. Evatt, Richard Levine, and Neil Williams.

The committee is grateful to the following companies whose participation greatly enhanced the success of the symposium: Beckman Instruments, Inc., Becton-Dickinson Co., Coulter Electronics, Inc., E. Leitz, Inc., Ortho Instruments, and Vickers Instruments, Inc. In addition, the committee is indebted to the members of the Hematology Division, CDC. They spent tireless hours assisting in the organization of the symposium and it was their efforts that made the meeting run smoothly. We extend our special thanks to Dr. Kathryn Kellar, Mrs. Neile McGrath, Rosemary Ramsey, Peggy Fett, Evelyn DuVal, and to Mr. Walter Scheffel of the Instructional Media Division.

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MEGAKARYOCYTE BIOLOGY AND PRECURSORS: IN VITRO CLONING AND CELLULAR PROPERTIES

Introduction

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MEGAKARYOCYTE BIOLOGY AND PRECURSORS:
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Megakaryocytopoiesis *In Vivo*

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Technological advances have profoundly influenced hemopoietic research in recent years by providing capabilities to isolate blood forming cells, study their physiology and chemistry, and grow clones of recognizable differentiated hemopoietic cells from morphologically unrecognizable stem cells. These new techniques should advance our understanding of hemopoiesis and its regulation, but it will be vital to determine how the findings in culture apply to hemopoiesis in intact organisms. Therefore, as a preamble to the first major conference on megakaryocytes *in vitro*, it is appropriate to review some of our knowledge and speculations about behavior of megakaryocytes *in vivo*.

Observations of platelet production and megakaryocytopoiesis in experimental animals and in human beings have led to certain concepts about the way that megakaryocytes develop from pluripotential stem cells (Fig. 1). The data are consistent with a model in which the cells become committed to megakaryocytopoiesis, but do not immediately differentiate further or enter into active proliferation. This compartment will be referred to as non-proliferating with the understanding that this terminology allows either for a small portion of cells to be in cycle or for all cells to be in cycle with a long generation time. Thereafter, the megakaryocyte precursors appear to undergo cellular proliferation and initiate nuclear replication without cell division before becoming recognizable as megakaryocytes. Nuclear replicative capacity persists in the most immature recognizable cells (Feinendegen et al., 1962), but the major activities in the recognizable compartment are related to cytoplasmic growth and development. Recognizable megakaryocytes are polyploid, and, in the normal steady state, the major classes of cells have 4, 8, and 16 times the normal diploid amount of DNA (Odell et al., 1965). Size of mega-

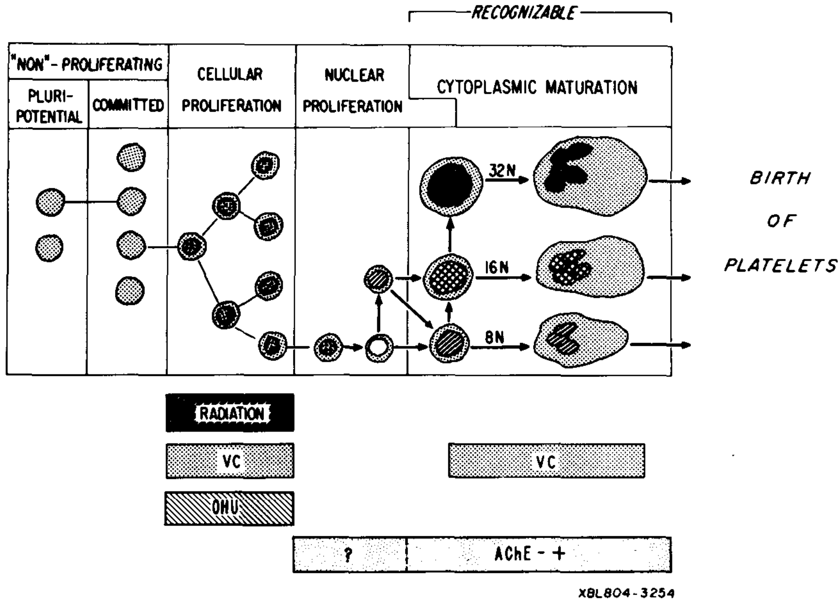

Fig. 1. Annotated model of megakaryocytopoiesis. Sites of major actions of cytotoxic agents are indicated (VC = vincristine; OHU = hydroxyurea). The area labeled AChE – + indicates cells that in rats or mice stain for the enzyme acetylcholinesterase; the ? indicates that some of the small cells undergoing nuclear proliferation may be small AChE – + cells.

karyocytes is proportional to ploidy (Odell et al., 1970), but the relationship of size and ploidy of a megakaryocyte to the number and size of platelets it produces is not clear (Paulus et al., 1979a).

It is convenient to think of these cells as compartmentalized, of the compartments as having well-defined boundaries, and to consider that the cells march through the compartments like soldiers. Such artificial notions are, in fact, consistent with some experimental observations. However, it is likely that the cells behave more in a civilian than military fashion and the lack of regimentation may become more apparent after perturbations than it is in the normal steady-state.

Platelet production has been found to be regulated, in part, by the number or mass of circulating platelets, but the relative importance of these two parameters of platelet concentration has not been established. It has been suggested that the total body mass of platelets may be a more important homeostatic parameter than is the number or mass of platelets in a given volume of circulating blood (Aster, 1966). In spite of these uncertainties, it is clear that deficiency of circulating platelets is associated with stimulation of megakaryocytopoiesis (Craddock et al., 1955) and an excess with its suppression (Cronkite, 1957). The homeostatic mechanisms affect megakaryocytic precursor cells, rather than recognizable megakaryocytes them-

selves, and this finding is consistent with the localization of proliferative activity largely to the precursor compartments. Cytotoxic agents that show their effect on proliferating cells also affect predominantly the precursor cells. By analyzing the ways in which homeostatic perturbations and cytotoxic agents, alone or in combination, ultimately affect recognizable megakaryocytes and platelet production, information about the precursor compartments can be gained.

It is known that pluripotential stem cells participate in the homeostatic response to thrombocytocytopenia. Their numbers increase in the spleens of thrombocytopenic mice, but not in the bone marrow (Ebbe et al., 1971). However, other observations suggest that homeostatic regulation of platelet production is mediated by committed precursor cells, thus implying that pluripotential stem cell changes may be secondary. For example, W/W^v mice are known to have a severe defect of pluripotential stem cells. Nevertheless, they respond to and recover from immunothrombocytopenia normally (Shreiner, 1976; Ebbe and Phalen, 1978). More convincing evidence that the homeostatic mechanisms do not affect the pluripotential stem cells directly comes from the experiments of Goldberg et al. (1977). They found that prevention of thrombocytopenia (by platelet transfusion) in lethally irradiated recipients of bone marrow transplants inhibited splenic megakaryocytopoiesis as measured 10 days later. This effect was found when platelet transfusions were given for the full 10-day period of observation or for only the final 4 days; it was not found when platelets were administered only on the first 2 days after irradiation and transplantation, a period when pluripotential stem cell seeding and proliferation occurs. Thus, suppression of megakaryocytopoiesis by high platelet counts, in these experiments, appeared to affect differentiation of precursor cells into recognizable megakaryocytes rather than pluripotential stem cell proliferation.

After exposure to sublethal doses of ionizing radiations, mouse platelet counts show characteristic changes (Ebbe and Stohlman, 1970). They are maintained at a normal level for 4 days, corresponding to continued production of platelets by radioresistant recognizable megakaryocytes and their immediate precursors. There is a subsequent 4-day period, corresponding to the mouse platelet survival time, during which the platelet count drops because production is reduced as a result of radiation-induced damage to a sensitive precursor compartment. Thereafter, recovery gradually occurs. It is noteworthy that onset of thrombocytopenia is preceded by megakaryocytopenia in the bone marrow, but that the recovery of platelet counts occurs while megakaryocytopenia persists (Ebbe and Phalen, 1979). The initial recovery may be mediated, in part, by the stimulatory effect of thrombocytopenia on the recovering megakaryocytes.

If megakaryocytopoiesis is acutely stimulated by induction of thrombocytopenia immediately before or after sublethal irradiation of the mice, the radiation-induced thrombocytopenia is reduced in severity and duration (Ebbe and Stohlman, 1970). Therefore, the stimulus of acute thrombocytopenia on day 0 must affect a population of precursor cells that was not heavily damaged by the radiation; the response of this population of cells appears to result in an earlier repopulation of the megakaryocytes. It seems likely that such a compartment of cells would be one that was

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