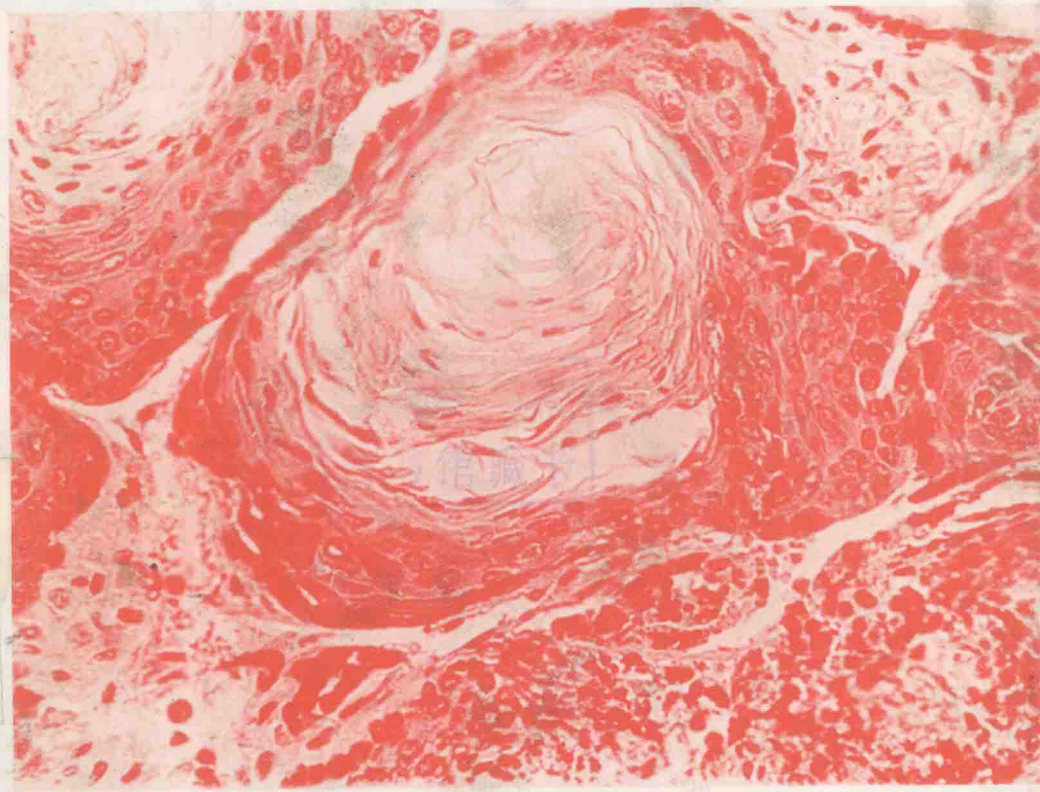
Biological Carcinogenesis



edited by
Marvin A. Rich and Philip Furmanski

BIOLOGICAL CARCINOGENESIS

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Marvin A. Rich and Philip Furmanski
AMC Cancer Research Center and Hospital
Lakewood, Colorado

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PREFACE

Neoplastic transformation can be induced by biological, chemical and physical agents. Are the mechanisms underlying carcinogenesis by these classes of agents the same, or are they as diverse as their properties are distinctive? Are the interactions which occur between the classes of carcinogens important factors in cancer causation and progression? And finally, can conceptual and technological advances made for one type of carcinogen be brought to bear on the resolution of the mechanistic mysteries which surround the others?

To address these questions, scientists in the forefront of viral, chemical and physical carcinogenesis, including those few individuals engaged in studies involving *combined modalities* of carcinogenesis, gathered in Detroit for a workshop on Biological Carcinogenesis, organized and supported by the Michigan Cancer Foundation and the National Cancer Institute.

In this volume, which originated from the Workshop presentations and discussions, the authors have identified the general principles which govern carcinogenesis by each of the major classes of carcinogens and determined to what extent these principles are applicable to the carcinogenic process induced by other classes of agents. There is described, in addition, current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive and thus, provide effective systems for the further study of this phenomenon.

To date, our mechanistic understanding of the carcinogenic process is painfully sparse and can ill afford less than optimum communication between those who study its diverse parts. It was

the aim of this workshop, and of this volume, to encourage and stimulate the full use of knowledge developed in one sphere of carcinogenic research by investigators in the others.

The editors and authors wish to thank the members of the Organizing Committee, Dr. Leila Diamond, Dr. Charles M. King, Dr. Charles M. McGrath and Dr. Louis R. Sibal for their enthusiastic participation in the development of the workshop, and the Michigan Cancer Foundation and the Division of Cancer Cause and Prevention of the National Cancer Institute of the United States for their support of the workshop.

Marvin A. Rich

Philip Furmanski

CONTRIBUTORS

LARRY O. ARTHUR *Biological Carcinogenesis Program, Frederick Cancer Research Center, Frederick, Maryland*

LAURE AURELIAN *Department of Biochemistry and Biophysics, Division of Comparative Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

P. A. BENTVELZEN *Radiobiological Institute TNO, Rijswijk, The Netherlands*

JANET S. BUTEL *Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas*

TIMOTHY H. CARTER *Department of Biological Sciences, St. John's University, Jamaica, New York*

ALAIN DECLEVE* *Cancer Biology Research Laboratory, Department of Radiology, Stanford University School of Medicine, Stanford, California*

JOSEPH E. DE LARCO *Laboratory of Viral Carcinogenesis, National Cancer Institute, Frederick Cancer Research Center, Frederick, Maryland*

SANDRA K. DUSING-SWARTZ *Department of Cell Biology, Baylor College of Medicine, Houston, Texas*

PAUL B. FISHER *Department of Microbiology, Cancer Center/ Institute of Cancer Research, College of Physicians and Surgeons, Columbia University, New York, New York*

PHILIP FURMANSKI† *Department of Biology, Michigan Cancer Foundation, Detroit, Michigan*

Current Affiliation: Risk Management Division, Stanford University School of Medicine, Stanford, California

†*Current Affiliation: AMC Cancer Research Center and Hospital, Lakewood, Colorado*

ROBERT C. GALLO *Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

RAYMOND V. GILDEN *Biological Carcinogenesis Program, Frederick Cancer Research Center, Frederick, Maryland*

NEIL I. GOLDSTEIN *Monell Chemical Senses Center, Philadelphia, Pennsylvania*

PHILIP L. GROVER *Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, London, United Kingdom*

RUSSELL EARL HAND, JR. *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

DAVID K. HOWARD *Life Sciences Division, Meloy Laboratories, Inc., Springfield, Virginia*

ELIEZER HUBERMAN *Toxicology and Carcinogenesis Program, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

CANDACE S. JOHNSON *Department of Biology, Michigan Cancer Foundation, Detroit, Michigan*

CAROL A. JONES *Toxicology and Carcinogenesis Program, Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

RICHARD F. JONES *Department of Tumor Biology, Michigan Cancer Foundation, Detroit, Michigan*

HENRY S. KAPLAN *Cancer Biology Research Laboratory, Department of Radiology, Stanford University School of Medicine, Stanford, California*

JAMES O. KIGGANS, JR. *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

V. KRUMP-KONVALINKOVA *Radiobiological Institute TNO, Rijswijk, The Netherlands*

MIRIAM LIEBERMAN *Cancer Biology Research Laboratory, Department of Radiology, Stanford University School of Medicine, Stanford, California*

RUEY-SHYAN LIOU *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

SIMONE MANTEUIL-BRUTLAG *Cancer Biology Research Laboratory, Department of Radiology, Stanford University School of Medicine, Stanford, California*

MARK MAMRACK *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

MARK M. MANAK *Departments of Biophysics and Comparative Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

JOHN MARCELLETTI *Department of Biology, Michigan Cancer Foundation, Detroit, Michigan*

CHARLES M. MCGRATH *Department of Tumor Biology, Michigan Cancer Foundation, Detroit, Michigan*

DANIEL MEDINA *Department of Cell Biology, Baylor College of Medicine, Houston, Texas*

JAMES A. OTTEN *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

MARVIN A. RICH* *Michigan Cancer Foundation, Detroit, Michigan*

JEFFREY SCHLOM *Laboratory of Cellular and Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

THOMAS J. SLAGA *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

GILBERT H. SMITH *Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

SUSAN H. SOCHER *Department of Cell Biology, Baylor College of Medicine, Houston, Texas*

HERBERT D. SOULE *Department of Tumor Biology, Michigan Cancer Foundation, Detroit, Michigan*

RAYMOND W. TENNANT† *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

GEORGE J. TODARO *Laboratory of Viral Carcinogenesis, National Cancer Institute, Frederick Cancer Research Center, Frederick, Maryland*

**Current Affiliation: AMC Cancer Research and Hospital, Lakewood, Colorado*

†Current Affiliation: National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

PAUL O. P. TS'O *Division of Biophysics, School of Hygiene and Public Health, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

D. W. VAN BEKKUM *Radiobiological Institute TNO, Rijswijk, The Netherlands*

K. VAN DEN BERG *Radiobiological Institute TNO, Rijswijk, The Netherlands*

TSE-WEI WANG *Biology Division, Oak Ridge National Laboratory, and the University of Tennessee - Oak Ridge Graduate School of Biomedical Sciences, Oak Ridge, Tennessee*

I. BERNARD WEINSTEIN *Department of Medicine/School of Public Health, and the Cancer Center/Institute for Cancer Research, College of Physicians and Surgeons, Columbia University, New York, New York*

WEN K. YANG *Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee*

C. S. H. YOUNG *Department of Microbiology, Institute for Cancer Research, College of Physicians and Surgeons, Columbia University, New York, New York*

HOWARD A. YOUNG *Biological Carcinogenesis Program, Frederick Cancer Research Center, Frederick, Maryland*

CONTENTS

MECHANISMS IN VIRAL CARCINOGENESIS

T-CELL GROWTH, T-CELL GROWTH FACTOR, T-CELL LEUKEMIAS AND LYMPHOMAS AND ISOLATION OF A NEW TYPE-C RETROVIRUS

Robert C. Gallo

Laboratory of Tumor Cell Biology
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

SUMMARY

About 5 years ago we discovered a new system for the long term (continuous) growth of normal human T-cells. These include T cells with functional activities. The cells are mature T-lymphocytes positive in E-rosette assays and negative for the enzyme terminal deoxyribonucleotidyl transferase. The growth of these cells can far surpass the finite number of generations described for normal fibroblasts, and the cells remain normal in all criteria. Their growth is strictly dependent upon a factor we call T-cell growth factor (TCGF). TCGF is a small protein which binds to the surface only of antigen (or lectin) activated normal T-cells. Thus, TCGF appears to be the direct mitogen in the immune response of all T-cells. So called lymphocyte activation by antigen or lectin involves at least two important mechanisms. Some T-cells must recognize the antigen/lectin and form functional TCGF receptors; other T-cells release TCGF. The latter appears to be mediated by a prior interaction of lectin/antigen with macrophage which release lymphocyte activation factor which in turn stimulates the subset of T-cells to release TCGF. This event is normally transient because TCGF production is temporary. However, T-cell growth can be maintained in the laboratory by the periodic TCGF addition to the cultured cells. In contrast to normal T-cells, neoplastic T-cells obtained from patients with certain T-cell leukemias and lymphomas contain TCGF receptors and so respond directly to TCGF

(without requiring lectin or antigen activation). Several novel cell lines from patients with cutaneous T-cell leukemias and lymphomas (Sezary syndrome and mycosis fungoides) were established with TCGF. In some cases the cells became independent of added TCGF but release into the media their own TCGF.

Some of the T-cell cultures continuously release a new type-C retrovirus. We call these viruses HTLV. They are unique (not related to any animal viruses), and to date specific for these diseases. Antibodies have been found in some human sera specifically reactive with HTLV proteins, including the first patient from whom HTLV was isolated. We propose that the abnormal proliferation characteristic of leukemias and lymphomas of mature T-cells may involve abnormalities in the TCGF T-cell interaction, and that HTLV may be involved in the pathogenesis of these diseases.

INTRODUCTION

In this report I will summarize results of experiments from our laboratory relating to control of proliferation of human T-cells both normal and neoplastic. I will also describe the isolation of new type-C retroviruses (RNA tumor viruses) from some of these cells and why we believe these represent the first unambiguous isolation of human retroviruses. Finally, I will formulate a working hypothesis for the mechanism of transformation of these cells. The studies which I will describe were in part carried out with my associates F. Ruscetti Ruscetti, B. Poiesz, J. Mier, M. Reitz, and V. Kalyanaraman, and portions of the work (those with clinical material from patient C. R.) were performed in collaboration with J. Minna and his colleagues P. Bunn and A. Gazdar, all of the NCI-VA Clinical Medical Oncology Branch in Washington, D.C.

The Continuous Growth of Normal Functional Mature Human T-Cells

The ability to continuously grow normal human mature T-cells in liquid suspension culture was achieved for the first time about 5 years ago [1,2]. This has been widely confirmed and extended (see especially work of K. Smith reviewed in [3], and is now almost routinely employed in laboratories interested in T-cell biology. The system has extremely interesting and important features. First of all, despite long

term culture the cells remain normal in karyotype, have functional (e.g., cytotoxic) activity, remain strictly dependent on a factor termed T-cell growth factor (TCGF) for their growth (see below) and do not produce tumors in nude mice. Second, the proliferation far exceeds the finite generations number of cell divisions believed to be the limit of proliferation of committed cells (Hayflick number), indicating that mature T-cells have stem cell features. Third, the cells can be cloned and used in numerous T-cell immunobiology experiments. Fourth, there is rationale for their clinical use. For example, by the combination of cloning techniques and the use of TCGF, autologous cytotoxic T-cells for a tumor may be obtained in large numbers and used in immunotherapy. In addition, the central role of TCGF in T-cell proliferation makes it seem likely to us that immune deficiencies due to diminished number of T-cells might be helped by exogenous TCGF. Fifth, the availability of purified TCGF [4,5] and its specific interaction with activated T-cells makes it possible to study the interaction of a pure growth factor with a cloned population of cells newly cultured from clinical specimens. Sixth, as discussed later, this system recently led to the establishment of several new kinds of neoplastic T-cell lines, and the available information suggests that T-cell-TCGF changes in the normal production and and/or response to TCGF may be involved in the abnormal proliferation characteristic of T-cell leukemias and lymphomas. Some of the new cell lines also led to the isolation of new kinds of type-C retroviruses (see below).

Components of the System

Normal leukocytes are obtained from blood, bone marrow or spleen and the mononuclear fraction separated from other leukocytes by nylon column chromatography [6,7]. The cells are stimulated with lectin/antigen (generally PHA). This leads to blastogenesis (activation) of a subset of T-cells involving synthesis of DNA, some cell division and if left as such termination of the culture. After the exposure to the lectin/antigen TCGF is released into the media, probably by a subset of T-cells different from those which respond to TCGF. Even-

tually, TCGF release ceases and the cultured cells terminate their growth unless there is intervention. Apparently, macrophages mediate the T-cell release of TCGF. After their interaction with lectin/antigen the macrophages release a factor termed lymphocyte activating factor which induces the T-cells to release TCGF. Thus, some adherent cells are required. If exogenous TCGF is added every 3 to 4 days to the cultured cells the T cells proliferate indefinitely (reviewed in [8]). It is now abundantly clear that with normal cells TCGF can only induce growth after the T-cells are activated. Only after antigen/lectin activation are receptors for TCGF available. A schematic illustration of these interactions is shown in Figure 1 and the properties of the normal cells in Table 1. For more detailed description and references see the recent review [8].

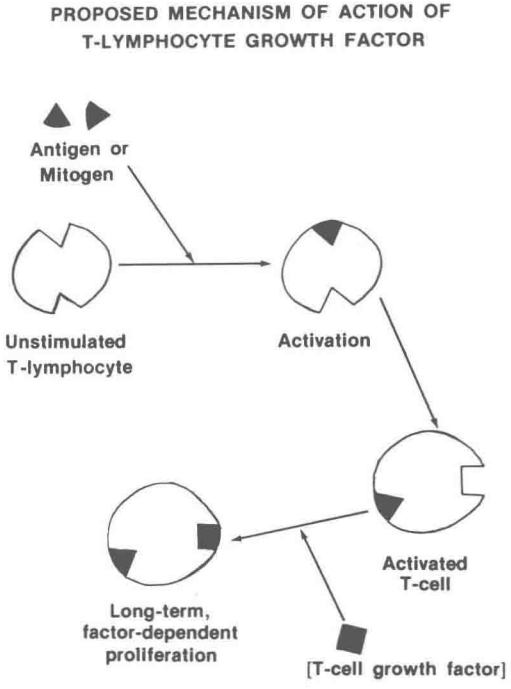

Figure 1. Simplified scheme for normal T-cell proliferation in response to antigen.