EICOSANOIDS AND RADIATION

PROSTAGLANDINS, LEUKOTRIENES, AND CANCER

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CONTRIBUTORS

CATRAVAS, G.N., Department of Radiation Biochemistry and Chair of Science, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145, U.S.A.

DAS, U.N., Department of Clinical Pharmacology and Medical Research, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad 500482, India.

DELEO, V., Department of Dermatology, Columbia University, 630 West 168th Street, New York City, New York 10032, U.S.A.

GOLDBERG, I.D., Department of Radiotherapy, Harvard Medical School, 50 Binney Street, Boston, Massachusetts 02115, U.S.A.

KLIGMAN, L.H., Department of Dermatology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania 19104, U.S.A.

KOT, P.A., Department of Physiology and Biophysics, Georgetown University Medical Center, 3900 Reservoir Road N.W., Washington, D.C. 20007, U.S.A.

LIM, H.W., Department of Dermatology, New York University School of Medicine, New York City, New York 10016, U.S.A.

MENCONI, M., Boston University School of Medicine, Department of Biochemistry, Boston, Massachusetts 02118, U.S.A

MITCHELL, M.D., Department of Reproductive Medicine, University of California - San Diego, La Jolla, California 92093, U.S.A.

POLGAR, P., Boston University School of Medicine, Department of Biochemistry, Boston, Massachusetts 02118, U.S.A.

RAMA DEVI, G., Department of Clinical Pharmacology and Medical Research, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad 500482, Andhra Pradesh, India.

RAMWELL, P.W., Department of Physiology and Biophysics, Georgetown University Medical Center, 3900 Reservoir Road N.W., Washington, D.C. 20007, U.S.A.

REICHEL, R., First Department of Gynecology and Obstetrics, University of Vienna, Spitalgasse 23, A-1097 Vienna, Austria.

ROSEN, E.M., Department of Therapeutic Radiology, Yale University Medical School, 333 Cedar Street, New Haven, Connecticut 06510, U.S.A.

RUBIN, D.B., Rush University Medical School, Department of Medicine, Rush Presbyterian St. Luke's Medical Center, Chicago, Illinois 60612 U.S.A.

SCHNEIDKRAUT, M.J., Department of Physiology and Biophysics, Georgetown University Medical Center, 3900 Reservoir Road N.W., Washington, D.C. 20007, U.S.A.

SINZINGER, H., Department of Nuclear Medicine and Atherosclerosis Research Group (ASF), University of Vienna, Schwarzspanierstrabe 17, A-1090 Vienna, Austria.

STEEL, L.K., Department of Radiation Biochemistry and Chair of Science, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145, U.S.A.

STRICKLAND, D.M., Division of Maternal and Child Health, Wilford Hall USAF Medical Center, San Antonio, Texas 78236, U.S.A.

VINTER, D.W., Department of Radiotherapy, Harvard Medical School, 50 Binney Street, Boston, Massachusetts 02115, U.S.A.

WALDMAN, J.S., Dermatology Section, N.Y. Veterans Administration Medical Center, New York City, New York 10016, U.S.A.

WEPPLEMAN, B., Department of Radiation - Oncology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, Alabama 35233, U.S.A.

FOREWORD

Prostaglandins, Leukotrienes, and Cancer is a multi-volume series that will focus on an emerging area of cancer research. In 1968, R.H. Williams first reported that elevated prostaglandin levels are present in human medullary carcinoma. Since that time, the concept that arachidonic acid metabolites may be involved in cancer has expanded to include every aspect of the disease from cell transformation through metastasis.

Prostaglandins and leukotrienes are generic terms used to describe a family of bioactive lipids produced from unsaturated fatty acids (principally from arachidonic acid) via the cyclooxygenase and lipoxygenase pathways, respectively. Cyclooxygenase products consist of diverse products such as prostaglandin E_2 (PGE_2), prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), whereas lipoxygenase products consist of hydroperoxy fatty acids and mono-, di- and tri-hydroxy acids including leukotrienes. The precursor fatty acids for the cyclooxygenase and lipoxygenase pathways are present in cellular phospholipids. This finding established an important control point in their biosynthesis—the release of substrate. This occurs in response to numerous stimuli that act at the cell surface. Dr. Bengt Samuelsson's extensive study of the metabolism of prostaglandins indicated that they are rapidly inactivated on a single pass through pulmonary circulation. Thus, they cannot act as circulating hormones and appear to be made on demand in or in the vicinity of target tissues leading to the concept that prostaglandins are local hormones or autocoids.

Altered production, qualitative and/or quantitative, of prostaglandins and leukotrienes has been implicated in the development of a number of disease states (e.g., atherosclerosis, inflammatory diseases, asthma). Evidence has been accumulating in the literature suggesting that prostaglandins and leukotrienes may stimulate or inhibit various steps in the complex etiology of cancer, i.e., steps in the progression from a transformed cell to a metastatic tumor. The initial volumes in this series will examine the roles of prostaglandins and leukotrienes in tumor initiation, tumor promotion, tumor cell growth and differentiation, tumor immunity, tumor metastasis and cancer therapy. We hope as this field of cancer research develops that this series, Prostaglandins, Leukotrienes, and Cancer, will provide a forum within the framework of current evidence for the synthesis of new hypotheses and discussion of controversial issues.

Kenneth V. Honn
Lawrence J. Marnett

PREFACE

Convincing evidence has now accumulated linking radiation and eicosanoid production. The reported radiation caused changes have varied from those showing overall increases in prostaglandin (PG) production, to shifts in the production of PG types, to general decreases in PG production. Because of the complexity of dosimetry, time of measurement after exposure to radiation and the given tissue or cell type, many of these apparent conflicting data may in reality represent differences in experimental conditions. Clearly, further experimental data is necessary to fully understand the process. What is important at this time is to recognize the fact that both ionizing and ultraviolet radiation may be affecting the synthesis of eicosanoids in a physiologically significant manner. Interestingly, data now exists suggesting that the presence of eicosanoids offers the organism protection from radiational injury. In light of these reports, it is conceivable that a better understanding of the interaction between eicosanoids and radiation will ultimately prove to be therapeutically beneficial.

In this volume, we present a comprehensive discussion of eicosanoids and radiation. We concentrate on ionizing and ultraviolet radiation, if for no other reason than that much of the existing data has focused on these two areas. As much as possible, we attempt to present data as it has developed, including conflicting results. The effect of ionizing radiation on eicosanoid metabolism is discussed in four chapters in terms of cells in culture, intact tissue, the whole organism and blood vessels. A similar approach is used to examine the effects of ultraviolet radiation on eicosanoid metabolism.

Evidence showing that eicosanoids afford the organism protection against both ionizing and ultraviolet radiation is discussed in a series of articles, including evidence that eicosanoids provide protection against genetic damage.

Radiation is generally viewed from the perspective of nucleus and chromosomal alterations. However, lipid peroxidation and the generation of reactive radicals may also be important factors in

the radiational effects on cell physiology. In fact, the generation of peroxide molecules and oxygen radicals are important elements in the regulation of a number of enzyme systems, including those associated with eicosanoid synthesis. This relationship is discussed in a separate chapter where we examine the influence of peroxides and oxygen radicals on both the cyclooxygenase and phospholipase A_2 enzyme systems. Finally, to place the eicosanoid story into perspective, the last two chapters discuss the radiobiology of blood vessels and the effect of ultraviolet radiation on the skin.

It is the aim of this volume to summarize and clarify the interactions between radiation and eicosanoids as they are presently understood.

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