

Oxidative Stress in Applied Basic Research and Clinical Practice

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Donald Armstrong

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Note from the Editor-in-Chief

All books in this series illustrate point-of-care testing and critically evaluate the potential of antioxidant supplementation in various medical disorders associated with oxidative stress. Future volumes will be updated as warranted by emerging new technology, or from studies reporting clinical trials.

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Oxidative Stress in Cancer Biology and Therapy

 Humana Press

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Preface

Oxidative Stress and Cancer Biology: A Historical Perspective

Driven by Warburg's observation of increased glucose metabolism in cancer cells [1] as well as decades of research in the first three quarters of the twentieth century by Weber and many other investigators (reviewed in [2, 3]), cancer was thought to have at its origins fundamental defects in glycolytic and respiratory metabolism. This theoretical construct was based on the proposal that cancer cells had fundamental defects in their respiratory processes (O_2 metabolism) that were believed to be compensated for by increases in glycolytic metabolism. This dependence on glycolysis was thought to keep cancer cells from being able to properly regulate the switching between glycolysis and respiration which was thought to inhibit the cancer cell's ability to engage in normal higher order differentiated cellular functions.

With the discovery of oncogenes [4, 5] and tumor suppressor genes [6] in the last quarter of the twentieth century the critical importance of the accumulation of genetic alterations in the process of carcinogenesis and maintenance of the malignant phenotype became clearly evident. In this theoretical construct, cancer is believed to be a multistep genetic disease in which mutations resulting in the aberrant expression of cellular homologues of oncogenes (i.e., Ras, c-Fos, c-Jun, and c-Myc, etc.) associated with growth and development as well as tumor suppressor genes (i.e., p53) gradually accumulated over time, eventually resulting in immortalization, the loss of control of cell proliferation, and progression to the malignant phenotype.

During the same era that the genetic theory of cancer was blossoming, Oberley et al. [7–10], formally proposed the Free Radical Theory of Cancer which incorporated critical aspects of both metabolic and genetic theories of cancer. In this theoretical construct, cancer cells were proposed to have aberrant mitochondrial respiration leading to increased steady-state levels of superoxide and hydrogen peroxide that caused damage (both genetic and epigenetic) leading to the activation of oncogenes that governed signaling pathways controlling the malignant phenotype. This proposal was then followed by the recognition that free radicals and reactive

oxygen species produced by O_2 metabolism could act as both initiators and promoters of carcinogenesis as well as contribute to the process of cancer progression [11–13]. Also it was confirmed that cancer cells appeared to exist in a chronic condition of metabolic oxidative stress characterized by increased steady-state levels of mitochondrial respiratory chain-dependent superoxide and hydrogen production [14–16] that stimulated signaling pathways affecting the malignant phenotype that were compensated for by increased levels of glucose and hydroperoxide metabolism [16–19]. At the end of the twentieth and the beginning of the twenty-first centuries, these and similar findings from other investigators have led to the realization that free radical biology and cancer biology are two integrally related fields of investigation that can greatly benefit from cross-fertilization of theoretical constructs.

The current volume of scientific reports was assembled under the heading of “Oxidative Stress in Clinical Practice: Cancer” in order to stimulate discussion of how the well-established role of oxidative stress in cancer biology as well as in mechanisms by which radiation therapy and chemotherapy kills cancer cells can be utilized to design interventions to enhance therapeutic responses while causing fewer treatment limiting complications. The data gathered in the last 30 years which is summarized in the chapters contained in this volume, supports the hypothesis that selective enhancement of oxidative stress in cancerous tissues based on fundamental differences in oxidative metabolism between cancer vs. normal cells can be used as a target for enhancing therapeutic outcomes as well as sparing damage to normal tissues. In addition, since oxidative stress is believed to be causally involved with initiation, promotion, and progression of carcinogenesis, interventions designed to limit oxidative stress may also hold promise for limiting the numbers of cancers that are induced as well as delaying the progression of cancers once they are formed.

Finally, we would also like to dedicate this volume of work to the memory of Dr. Larry W. Oberley (1946–2008) who was the originator of the Free Radical Theory of Cancer [7–10]. Dr. Oberley diligently championed this theoretical construct during the difficult early phases of development when the field of study was being established. He also involved his students, colleagues, and junior faculty collaborators at every step of the way in his academic journey, which resulted in Dr. Oberley being integrally involved with training and mentoring of a generation of Free Radical Cancer Biologists. Dr. Oberley was an exceptional theoretician, scientist, and educator whose many contributions to the study of oxidative stress in cancer biology are clearly evident in the excellent chapters contained in this volume.

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