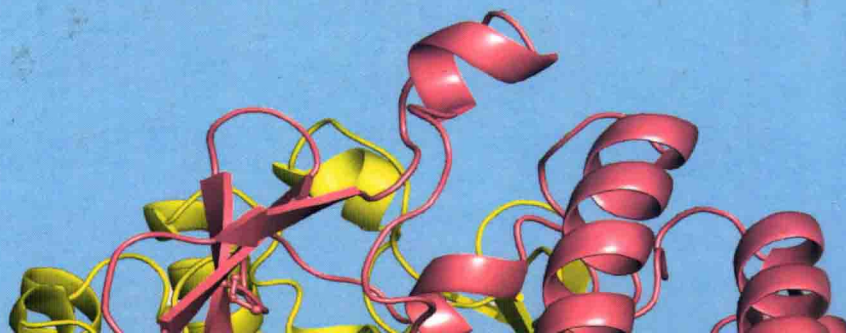




Molecular Basis of Oxidative Stress

Chemistry, Mechanisms, and Disease Pathogenesis

EDITED BY
FREDERICK A. VILLAMENA



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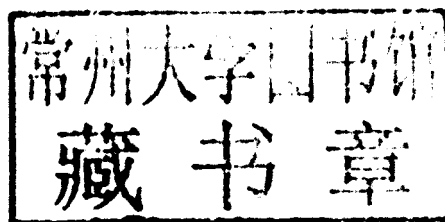
MOLECULAR BASIS OF OXIDATIVE STRESS

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Department of Pharmacology and Davis Heart and Lung Institute
The Ohio State University
Columbus, Ohio



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MOLECULAR BASIS OF OXIDATIVE STRESS

PREFACE

That life as we know it is built from but a handful of elements suggests that despite the necessary complexity of biomolecules to store and relay information, it is still highly regulated by one simple molecule—oxygen. More simply, if one theme can be reduced from the vastly circuitous biochemistry of the living cell, it is that of oxygen regulation. At the heart of this highly regulated system is the relatively predictable behavior of the key biological oxido-reductants. Most typical oxido-reductants are the reactive species of oxygen, nitrogen, sulfur, and halogens. Due to their highly reactive nature, these species can be difficult to observe; however, they are increasingly understood to play a key role in the regulation of vital cellular processes such as in proliferation, intracellular transport, cellular motility, membrane integrity, immune responses, and programmed cell death. Formed as by-products of the metabolism of oxygen, reactive species are regulated by powerful antioxidant defense systems within the cell to minimize their damaging effects. However, the imbalance between the pro-oxidant and antioxidant defense mechanisms of the cell or organism in favor of the former can result in oxidative stress. Prolonged oxidative stress conditions lead to the pathogenesis of various diseases such as cancer, neurodegeneration, cardiovascular, and pulmonary diseases to name a few.

In a most abstract sense, life itself is a cascade of events originating from the very fundamental nature of the electron, to the reactivity of molecules on which electrons reside, to the chemical modifications that these reactions cause to biomolecular systems that can lead to a variety of intracellular signaling pathways. Such communication signals the survival or death of the cell, and ultimately that of the whole organism. Thus, it follows that the most fundamental causes of disease are reactive species.

The goal of this book is to provide comprehensive coverage of the fundamental basis of reactivity of reactive species (Chapter 1) as well as new mechanistic insights on the initiation of oxidative damage to biomolecules (Chapters 2–4) and how these oxidative events can impact cellular metabolism (Chapters 5–8) translating into the pathogenesis of some disease states (Chapters 9–13). This field of study could hopefully provide opportunities to improve disease diagnosis and the design of new therapeutic agents (Chapters 14–15).

Frederick A. Villamena

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D. Allan Butterfield was born in Maine. He obtained his PhD in Physical Chemistry from Duke University, followed by an NIH Postdoctoral Fellowship in Neurosciences at the Duke University School of Medicine. He then joined the Department of Chemistry at the University of Kentucky in 1975, rising to Full Professor in eight years. He is now the UK Alumni Association Endowed Professor of Biological Chemistry, Director of the Center of Membrane Sciences, Director of the Free Radical Biology in Cancer Core of the UK Markey Cancer Center, and Faculty of the Sanders-Brown Center on Aging at the University of Kentucky. He has published more than 550 refereed papers on his principal NIH-supported research areas of oxidative stress and redox proteomics in all phases of Alzheimer disease and in mechanisms of chemotherapy-induced cognitive dysfunction (referred to by patients as "chemobrain"). His chapter contribution was coauthored by Rukhsana Sultana and Giovanna Cenini.

Giovanna Cenini received her PhD in Pharmacology from the University of Brescia in Italy. After spending two years in the Butterfield laboratory as a predoctoral fellow and two years as a postdoctoral scholar, Dr. Cenini is now a postdoctoral scholar in Biochemistry at the University of Bonn. She has published approximately 15 papers from her time in the Butterfield laboratory mostly on oxidative stress and p53 in Alzheimer disease and Down syndrome.

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Sean S. Davies was born in Honolulu, Hawaii. He obtained his PhD in Experimental Pathology from the University of Utah, followed by a postdoctoral fellowship in Clinical Pharmacology at Vanderbilt University, where he is now an Assistant Professor of Pharmacology. His research centers on the role of lipid mediators in chronic diseases including atherosclerosis and diabetes with an emphasis on mediators derived nonenzymatically by lipid peroxidation. His goal is to develop pharmacological strategies to modulate levels of these mediators and thereby treat disease. His chapter contribution was coauthored with Lili Guo.

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NIH-supported research areas of oxidative stress and lung disease. He is also a founder of Aeolus Pharmaceuticals and inventor on its product pipeline. He currently serves as Chief Scientific Officer for Aeolus Pharmaceuticals that is developing metalloporphyrins as therapeutic agents. His chapter contribution was coauthored by Neal Gould.

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Susan Flynn received her BS in Medicinal Chemistry and B.A. in Chemistry and from SUNY-University at Buffalo, and her doctoral research focuses on determining the substrate reactivity requirements for *in vivo* posttranslational modification and activation of associated cellular pathways.

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Alexandros G. Georgakilas is an Associate Professor of Biology at East Carolina University (ECU) in Greenville, NC and recently elected Assistant Professor at the

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Thomas B. Kryston, was born in Saint Petersburg, Florida, and received his MS in Molecular Biology and Biotechnology at East Carolina University. His graduate work focused on Oxidative Clustered DNA Lesions as potential biomarkers for cancer. Following his graduate studies, he was employed by The Mayo Clinic where his research interests were with Hexanucleotide expansions in ALS patients.

Yunbo Li is a professor and chair of the Department of Pharmacology and assistant dean for biomedical research at Campbell University School of Osteopathic Medicine. He is an adjunct professor at the Department of Biomedical Sciences and Pathobiology at Virginia Polytechnic Institute and State University, and an affiliate professor at Virginia Tech-Wake Forest University School of Biomedical Engineering and Sciences. He currently serves as Co-Editor-in-Chief for *Toxicology Letters* and on the editorial boards of *Cardiovascular Toxicology*, *Experimental Biology and Medicine*, *Molecular and Cellular Biochemistry*, *Neurochemical Research*, and *Spinal Cord*. Dr. Li is an active researcher in the areas of free radicals, antioxidants, and drug discovery, and the author of over 100 peer-reviewed publications and two recent monographs: *Antioxidants in Biology and Medicine: Essentials, Advances, and Clinical Applications*; and *Free radical Biomedicine: Principles, Clinical Correlations, and Methodologies*. The research in his laboratories has been funded by the United States National Cancer Institute (NCI), National Heart, Lung and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), American Institute for Cancer Research (AICR), and Harvey W. Peters Research Center Foundation. Dr. Li was joined by Hong Zhu, Jianmin Wang, and Aben Santo in his chapter.

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Aimin Liu was born in China. He obtained his PhD from Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences and from Stockholm University.

He did postdoctoral research at Xiamen University, University of Newcastle upon Tyne, and University of Minnesota. He started his independent research career at University of Mississippi Medical Center in October 2002, rising to Associate Professor in 2008 with tenure. He joined the chemistry faculty of Georgia State University in 2008 and was promoted to tenured Full Professor in 2012. He has published more than 60 refereed papers reporting mechanisms of oxygen activation by metalloproteins and metal-mediated signal transduction. His chapter is coauthored by Imran Rehmani and Fange Liu.

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Pharmacy at the University of Colorado, USA. After completion of an NIEHS-IRTA postdoctoral fellowship, he followed with Assistant Professor positions at the Department of Nutrition and the School of Community Health Sciences at the University of North Carolina-Chapel Hill, USA and the University of Nevada-Reno, USA, respectively. Currently, he has joined the Laboratory of Pathological Anatomy, University of Ioannina, Greece where he is an Assistant Professor of Molecular Pathology. His research encompasses the role of oxidative stress and natural products in cancer formation and prevention, respectively.

Aglaia Pappa was born in Ioannina, Greece and received her PhD in Biological Chemistry & Pharmacology from the University of Ioannina, Greece. After completion of a postdoctoral training at the School of Pharmacy, University of Colorado, USA, she has joined the Department of Molecular Biology & Genetics, Democritus University of Thrace, Greece as an Assistant Professor of Molecular Physiology & Pharmacology. Her research encompasses the role of oxidative stress in human disease, including carcinogenesis.

Sampath Parthasarathy obtained his PhD degree from the Indian Institute of Science, Bangalore, India in 1974. He spent one year at the Kyoto University, Japan as a postdoctoral fellow and subsequently joined the Duke University at Durham, NC. He then joined the Hormel Institute, University of Minnesota and became an Assistant Professor. From 1983–1993 Dr. Parthasarathy was a member of the faculty and reached the rank of professor at the University of California at San Diego. He developed the concept of oxidized LDL with his colleagues. In 1993, he was invited to become the Director of Research Division in the Department of Gynecology and Obstetrics at Emory University as the McCord-Cross professor. After serving 10 years at Emory, he joined Louisiana State University Health Science Center at New Orleans in November 2003 as Frank Lowe Professor of Graduate Studies and as Professor of Pathology. During 2006–2011, he served as the Klassen Chair in Cardiothoracic Surgery at the Ohio State University and was instrumental in developing a large animal model of heart failure. Currently, he is the Florida Hospital Chair in Cardiovascular Sciences and serves as Associate Director of Research at the Burnett School of Biomedical Sciences at the University of Central Florida in Orlando. Dr. Parthasarathy has published over 240 articles and has also written a book *Modified Lipoproteins in the Pathogenesis of Atherosclerosis*.

Mark T. Quinn was born in San Jose, CA and received a PhD in Physiology and Pharmacology from the Uni-

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Annmarie Ramkissoon obtained her PhD in toxicology in 2011 from the University of Toronto, where she focused upon drug bioactivation and antioxidative responses in neurodegeneration. Dr. Ramkissoon received several honors including a national graduate student scholarship from the Canadian Institutes of Health Research (CIHR) and the Rx&D Health Research Foundation. She is currently a postdoctoral fellow in the Division of Oncology in the Cancer and Blood Diseases Institute at the Cincinnati Children's Hospital Medical Center.

Imran Rehmani was born in St. Louis, Missouri. He obtained his Bachelors degree at the University of Mississippi in 2007. He researched at Georgia Tech and Georgia Health Sciences University before entering Georgia State University in 2010 under the advisement of Aimin Liu. He recently graduated with an MS in Chemistry. He will be joining Centers for Disease Control and Prevention as an ORISE research fellow.

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Jay L. Zweier was born in Baltimore, Maryland, and received his baccalaureate degrees in Physics and Mathematics from Brandeis University. After PhD training in Biophysics at the Albert Einstein College of Medicine, he pursued medical training at the University of Maryland, School of Medicine and received his MD in 1980. Subsequently, he completed his residency in internal medicine followed by his cardiology fellowship at Johns Hopkins University. In 1987, he joined the faculty of The Johns Hopkins University School of Medicine. In 1998, he was promoted to the rank of Professor and in 2000 was appointed as Chief of Cardiology Research, at the Johns Hopkins Bayview Campus. He was elected as a fellow in the American College of Cardiology in 1995 and the American Society of Clinical Investigation in 1994. In July of 2002, Dr. Zweier joined The Ohio State University College of Medicine as Director of the Davis Heart & Lung Research Institute and the John H. and Mildred C. Lumley Chair in Medicine. Dr. Zweier is currently Professor of Internal Medicine, Physiology, and Biochemistry, Director of the Center for Environmental and Smoking Induced Disease and the Ischemia and Metabolism Program of the Davis Heart & Lung Research Institute. He has published over 400 peer-reviewed manuscripts in the fields of cardiovascular research, free radical biology, and magnetic resonance.

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