Oxidative Stress in Aging

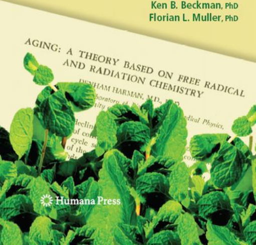
From Model Systems to Human Diseases

Edited by

Satomi Miwa, PhD

Ken B. Beckman, PhD

Florian L. Muller, PhD



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Preface

Aging remains one of the biggest unsolved problems in biology. More than 50 years ago, Denham Harman proposed the free radical theory of aging, arguing that cumulative damage from oxygen free radicals was causal to the process of aging. The fundamental idea is simple, yet scientifically plausible. Although at first it received limited attention, a recent explosion of investigative interest and endeavors has made the free radical theory the most extensively tested of all aging theories. The body of literature is now so vast and encompasses so many different techniques and model systems that an integrated evaluation of the evidence is difficult to say the least. Our goal in writing *Oxidative Stress in Aging: From Model Systems to Human Diseases* was to provide an easily accessible assessment of the free radical theory. We believe that the reader will find our "model system by model system" approach helpful, for it greatly simplifies a sometimes contradictory body of evidence.

A further development for the free radical theory is the realization that oxidative stress may contribute not only to aging per se, but also to the pathogenesis of a variety of age-related diseases. No assessment of the free radical theory of aging would be complete without an up-to-date account of major trends on the role of oxygen free radicals in the pathology of age-related diseases.

We thank all the contributors for taking time to produce outstanding chapters that not only summarize key data but also provide critical evaluation, discussion, and interpretation. This book is only possible because of their efforts.

We are also grateful to Dr. Matthew Ford for help with proofreading, and to Springer, particularly Richard Lansing, for exceptionally efficient help and advice throughout, and for accepting our demanding requests, one after another.

Satomi Miwa
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Section I
Introduction

1
Introduction

Satomi Miwa, Florian L. Muller, and Kenneth B. Beckman

1 Living in the Presence of Oxygen

The earliest life—simple cells—appeared 4 billion years ago, and rocks 3.5 billion years old contain microfossils of primitive one-celled organisms, the prokaryotes. At that time, the atmosphere contained little oxygen, and all life was anaerobic. About 3 billion years ago, photosynthetic blue-green algae (cyanobacteria) appeared, which slowly and eventually (800 million years later) raised atmospheric oxygen concentration [1, 2]. The rise in oxygen tension in the atmosphere coincides with development of complex eukaryotic life [3–5], and the Cambrian explosion, a profound diversification of animal life approximately 540 million years ago, occurred when oxygen reached concentrations close to those of today (21%) [6, 7]. Indeed, molecular and genetic analyses suggest a correlation, during the past 2.3 billion years, between the development of aerobic metabolism and increased organism complexity [4]. Aerobic metabolism using oxygen (oxidative phosphorylation) in mitochondria is highly efficient in generating energy from organic compounds, and mathematical analysis has shown that the presence of molecular oxygen in metabolic pathways allows far more complex reactions to occur than in those without oxygen [8]. According to one hypothesis, eukaryotes emerged after the engulfment of respiring bacteria (symbionts) by ancient anaerobic bacteria (hosts) – the symbionts being the origin of mitochondria [9]. Thus, the ability to perform oxidative metabolism is seen as a crucial factor in the emergence of complex multicellular life and evolution of animals. Oxidative metabolism remains the major form of energy production in virtually all animals today. Another significance of the appearance of oxygen in the atmosphere was the formation of the ozone layer, which protected the land from lethal levels of UV radiation.

However, despite its many beneficial effects, the emergence of oxygen as a major constituent of the atmosphere has presented all life forms living in its presence with a fundamental problem: how to efficiently protect themselves from its toxicity. In fact, many of the primitive anaerobic organisms are thought to have had died out when atmospheric oxygen levels rose. The only survivors were those species that evolved efficient mechanisms to detoxify oxygen, and those that colonized anaerobic or microaerobic environments [10, 11].

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