Integration of Metabolism, Energetics, and Signal Transduction

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Unifying Foundations in Cell Growth and Death, Cancer, Atherosclerosis, and Alzheimer Disease

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DEDICATION

This book is dedicated to my wife Elaine; my sons Jim, Matt, and Peter; my brother Steve; and to my parents, the late Lee and Sara Ockner.

PREFACE

Complex and unexplained phenomena tend to foster unorthodox perspectives. This publication is an example, as is a prior publication that emphasized the concept that intermediary metabolism might play a significant and determining role in hepatocyte proliferation and tumorigenesis[1]. Formulation of this hypothesis was based on an attempt to clarify several poorly understood phenomena; including the observations: 1) that xenobiotic peroxisome proliferators such as the fibrate hypolipidemic agents induce hepatocyte proliferation and carcinogenesis in rodents; 2) that benign and malignant liver tumors complicate the human syndrome of glycogen storage disease type I (glucose-6-phosphatase deficiency); and 3) that in this same syndrome, administration of glucose exerts an anti-tumor effect. Fatty acid and glucose metabolism are tightly linked in a well-established and profoundly inportant interplay. This connection, together with the fact that peroxisome proliferator-induced hepatocyte proliferation and carcinogenesis reflects inhibition of mitochondrial carnitine palmitoyltransferase-I and fatty acid oxidation, suggested the possibility that regulation of fatty acid metabolism could prove to be a pivotal determinant in the control of cell growth.

In 1993, the year in which the paper cited above was published, insight into the importance of growth factors and signal transduction pathways in cell cycle regulation was increasing rapidly, but metabolic and energetic aspects of cell proliferation had attracted relatively little attention. Despite this, the concept seemed inescapable that the two seemingly distinct and unrelated determinants — signal transduction and metabolism — were integrally linked. Moreover, it is known that growth regulation in the earliest eukaryotes was governed largely or exclusively by nutritional, metabolic, and energetic factors hundreds of millions of years before the appearance of intercellular signaling in higher organisms. It seemed

plausible, therefore, that these factors had retained a dominant regulatory role, at least under certain conditions, throughout the evolution of today's more advanced and complex species. What has emerged through the development of this treatise is evidence strongly suggesting that metabolism and energetics, while at times referred to as "housekeeping" functions, are intimately and directly linked to those signal transduction pathways that are essential to survival of the cell, the organism, and the species.

Initial work on the project (later to become Part II of the present volume) involved review of published contributions of many insightful and productive scientists. These addressed a broad range of relevant issues, including intermediary metabolism, signal transduction, and cell cycle regulation, and the effects of alternative substrates on mitochondrial energetics. Our preliminary[2] and unpublished experiments addressed the effects of endogenous and xenobiotic growth modulators on fatty acid metabolism and mitochondrial function, and provided critically important early insight and stimulus.

Unexpectedly, it also became appreciated during this time that, despite suppression of glucose utilization in brain regions affected by Alzheimer disease, neurons in those regions remained viable. Viewed in the context of the current project, this otherwise seemingly unrelated observation suggested the possibility that utilization of alternative substrates might also prove to be a critical determinant in the energetics, function, and injury of the neuron. Pursuit of published research related to this hypothesis led to the recognition of what appeared to be important parallels in intermediary metabolism and signal transduction between neuronal activation (Part III of this volume) and cell proliferation (Part II). Initially, Parts II and III were developed as separate analytical reviews. With the passage of time, however, their sustained growth in size, scope, and relatedness made separate publication less feasible and less desireable. As a result, they are included in the present combined format, along with short introductory and concluding sections (Parts I and IV, respectively) that provide overall perspective.

As work on the project progressed, it required ongoing review of increasing numbers of new publications in diverse fields; those findings most relevant to the integrated approach were selected for incorporation. Encouragingly, few published reports offered serious challenge to the present interpretations and hypotheses; of those, the more important are cited and discussed. Moreover, with continuing development of the project, its fundamental concepts became applicable to a growing number of surprisingly diverse additional areas, ranging from an early focus on liver regeneration to include programmed cell death[3], cancer cachexia, atherosclerosis, ischemia-reperfusion injury, regulation of feeding behavior, aspects of synaptic function, and the pathogenesis of Alzheimer disease.

While their broad relevance has provided additional support to many of the concepts, it has also required considerable stringency in the selection of publications for citation. As the regrettable but inevitable result, it was not possible to include reference to numerous other excellent publications that seemed less related to the present focus or less essential to its development. In any case, the project's very nature dictates that it will remain a work in progress.

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CONTENTS