NAVIGATING METABOLISM

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NAVIGATING METABOLISM

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Front cover artwork: This rendering of a cell illustrates the metabolism of glucose, fatty acids, and amino acids through glycolysis and mitochondria and symbolizes this book's exploration of how anabolic and catabolic pathways are used for bioenergetics, biosynthesis, and signal transduction.

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I dedicate this book to the previous and present members of my laboratory, who inspired me to write it. They provided the initial ideas for the tone and topics and helped edit the final proofs.

Contents

Common Abbreviations

These common abbreviations are used without definition throughout the book.

acetyl-CoA	acetyl coenzyme A
AMP	adenosine 5′-monophosphate
ADP	adenosine 5′-diphosphate
ATP	adenosine 5′-triphosphate
ATPase	adenosine triphosphatase
CMP	cytidine 5′-monophosphate
CDP	cytidine 5′-diphosphate
CTP	cytidine 5′-triphosphate
CO_2	carbon dioxide
CoA	coenzyme A
FAD	flavin adenine dinucleotide
$FADH_2$	reduced form of flavin adenine dinucleotide
GMP	guanosine 5′-monophosphate
GDP	guanosine 5′-diphosphate
GSH	glutathione
GSSH	oxidized form of glutathione
GTP	guanosine 5′-triphosphate
H_2O_2	hydrogen peroxide
NAD^+	nicotinamide adenine dinucleotide phosphate
NADH	reduced form of nicotinamide adenine dinucleotide phosphate
$NADP^+$	nicotinamide adenine dinucleotide phosphate
NADPH	reduced form of nicotinamide adenine dinucleotide phosphate
O_2^-	superoxide
ROS	reactive oxygen species
SOD	superoxide dismutase
TCA	tricarboxylic acid
TDP	thymidine 5′-diphosphate
TMP	thymidine 5′-monophosphate

TTP	thymidine 5′-triphosphate
UCP	uncoupling protein of the mitochondrial inner membrane
UDP	uridine 5′-diphosphate
UMP	uridine 5′-monophosphate
UTP	uridine 5′-triphosphate

Foreword

In the 20th century, studies of cellular and organismal metabolism led to the delineation of how nutrients were catabolized intracellularly to produce life-sustaining levels of ATP by the combined activities of enzymes involved in intermediate metabolism and the citric acid cycle. This golden age of metabolism ended with the crowning discovery of mitochondrial oxidative phosphorylation by Peter Mitchell in the 1960s. The elucidation of ATP generation was one of the greatest collective achievements of modern science and remains until this day the foundation of all biochemistry textbooks written for high school, college, and graduate students. However, by 1978, when Mitchell was awarded his Nobel Prize, biologists armed with the tools of molecular biology had moved on to studying gene expression, signal transduction, cell division, and differentiation. The fact that these processes were all anabolic and resource-intensive was largely ignored.

It was only at the start of the 21st century that it became apparent that the previous century's scientific stars had not quite worked out how metabolism was reprogrammed to support net macromolecular synthesis and cellular/organismal growth. Although individual scientists have been recognized for elucidating how nucleic acids, lipids, and amino acids were synthesized, the pathways they elucidated were viewed as homeostatically regulated branches of traditional intermediate metabolism.

During the last 15 years, the view that nutrient uptake and metabolism is regulated through cell-autonomous homeostatic mechanisms has been challenged by the discovery that signal transduction can directly influence nutrient uptake. For example, receptor-activated kinases were shown to directly induce nutrient uptake and metabolism. Furthermore, subsequent studies of the impact of nutrient uptake and availability on gene expression have demonstrated that the levels of intermediate metabolites can in turn regulate chromatin organization, gene expression, and protein translation. In turn, there is also a growing appreciation that signal transduction–initiated, transcriptionally induced variations of enzyme expression levels can influence intracellular metabolite flux into anabolic versus catabolic fates.

The integration of the role of anabolic metabolism in cell signaling and gene expression is still in its infancy. In *Navigating Metabolism*, Navdeep Chandel provides the reader with the conceptual framework through which to understand the evolving concepts that are reshaping and revitalizing metabolite biochemistry. Chandel brings a fresh perspective to metabolism, as he is equally comfortable and conversant in traditional biochemistry, bioenergetics, molecular biology, and signal transduction. Furthermore, the book provides readers with compelling examples of how Chandel and other scientists (Chapter 12) have drawn from these fields to reexamine how alterations in cellular/organismal metabolism contribute to the pathogenesis of diseases, including diabetes, cancer, and neurodegeneration. *Navigating Metabolism* is not meant to replace existing biochemistry textbooks, but rather to enhance and provide an update for all who are interested in the emerging concept of how metabolism is integrated with the rest of modern biology.

Craig B. Thompson
Memorial Sloan Kettering Cancer Center

Preface

TODAY THE STUDY OF METABOLISM IS enjoying a renaissance. It might not be evident to some of the younger readers but not so long ago metabolism was relegated to the background of scientific endeavors. How did metabolism make a comeback? I can only offer my own personal journey as an illustration of what I think excited many of the scientists to reengage with metabolism. In 1989, I was in the midst of my undergraduate student studies in mathematics at the University of Chicago. During the summer, I joined a biology laboratory to pay the bills so that I could spend the summer in Chicago. My project was to examine whether 3-phosphoglycerate could prevent hypoxia (low oxygen)-induced cell death. As a mathematician, I found that metabolism had a great appeal to me because metabolic pathways have an inherent logic dictated by thermodynamics. I continued working on metabolism in Paul Schumacker's laboratory as a graduate student, and my thesis examined the effects of hypoxia on the kinetics of the mitochondrial enzyme cytochrome *c* oxidase.

By the mid-1990s it was clear to me that most of my colleagues had very little interest in metabolism or any of my experiments. Most graduate students and postdocs at that time were excited about genetics, molecular biology, and signal transduction. But soon I was exposed to two ideas that for me connected metabolism to the rest of biology. First, while playing soccer, I met Craig Thompson, and he told me about an exciting finding from Xiaodong Wang's laboratory regarding the release of cytochrome *c* from mitochondria as an essential step in activating caspases resulting in death of mammalian cells. Craig's laboratory already had been studying metabolism in the context of growth factor regulation of apoptosis, and now his laboratory was further invigorated by Xiaodong's findings. My initial response was that the release of cytochrome *c* from mitochondria was an artifact. It was hard for me to imagine that cytochrome *c* was doing anything else other than being a substrate for cytochrome *c* oxidase. I just could not imagine that cytochrome *c* had another function outside the mitochondria, as the key signal to execute cell death. Of course, Craig had already seen the broad implications and connections of metabolism to biology beyond apoptosis. Soon, I was immersed in Craig's world of connecting metabolism

to biology, primarily by working with a talented graduate student in his laboratory, Matthew Vander Heiden. Matt explained the details of apoptosis to me, and soon we were engaged in daily conversations about the cross talk between apoptosis and metabolism, which in retrospect was instrumental in shaping my views on metabolism—not as an isolated discipline but connected to fundamental cellular decisions like "whether to live or die."

The second idea that brought my myopic vision of metabolism from biochemical pathways to metabolisms's vivid interaction with the rest of biology was an introduction to hypoxic gene expression by the late Eugene Goldwasser. Luckily, Emin Maltepe, a soccer buddy and graduate student in Celeste Simon's laboratory, was engaged in the first knockout of the transcription factor hypoxia-inducible factor (HIF), which is essential for induction of hypoxic genes. Emin explained the importance of HIF to me, and it was not very long before Paul, Emin, Celeste, Eugene, and I were all engaged in linking mitochondria to HIF. The idea that mitochondria could regulate gene expression further solidified my interest in pursuing the connection of metabolism to the rest of cell biology. When I had finished my postdoc in late 1999 and embarked in setting up my own laboratory in January of 2000, it was clear to me that going forward the excitement about metabolism revolved around integrating it to the rest of biology, physiology, and disease. Mitochondria were now more than bioenergetic and biosynthetic organelles—they were signaling organelles! Thus, the cross talk of metabolism to biology has reenergized this "ancient" discipline.

In the past decade, examining metabolism and its links to many biological outputs has intrigued many seasoned investigators along with new generations of students and postdocs. But most have found revisiting their biochemistry books quite intimidating. I flirted with the idea of writing a simple introduction to metabolism book with a conceptual framework of metabolic pathways and their links to the rest of biology, a book that would not replace many of the spectacular existing biochemistry textbooks but would complement them by illustrating how biochemistry comes alive through metabolism's connection to biology, physiology, and disease. However, one of the edicts of being a research scientist is not to engage in writing a single-author book. The daily pressure to get grants, publish, and do innovative work is challenging enough. So it was just my luck that I tagged along as an uninvited guest with Doug Green and met Richard Sever, Assistant Director and Acquisition Editor of Cold Spring Harbor Laboratory Press. Richard had been contemplating a similar idea, and before long I was writing my first book! It was quite challenging to get started and stay the course to the finish line. Luckily, I had Judy Cuddihy as an editor. Judy brought her vast experience in publishing to shape this book. Importantly, I am very grateful to her because throughout this process she has been both a coach and fan cheering me to the finish line. The artwork in this book is vital to making metabolism engaging, and I am appreciative to Pete Jeffs for his spectacular figures throughout the book. *Navigating Metabolism* should be viewed

as a wonderful collaboration between Judy, Pete, and me. I am also grateful to the staff at Cold Spring Harbor Laboratory Press, especially Inez Sialiano, Project Manager, and Kathleen Bubbeo, Senior Production Editor. I realize some might be disappointed that I did not cover certain topics nor provide enough detail, but the objective here was to provide an accessible introductory book to reengage a broad range of investigators with metabolism.

Finally, there are a few people who have contributed immensely to creating this book. My friend and colleague Ralph DeBerardinis wrote a fantastic appendix on metabolomics for the book and has been very supportive throughout the past year. The present and past members of my laboratory have provided wonderful ideas and helped edit the proofs. I am thankful to David Sabatini for insisting my original titles for the book were not very engaging and to Gerard Evan for providing the clever title *Navigating Metabolism*. And I am indebted to the 11 authors who contributed to Chapter 12, "Future Pathways of Metabolism Research." Chapter 12 provides a sense that there is still much to be learned about how metabolism connects to biology. Most of all, I am thankful to my daughter Anjali and my wife Evangelina for their love and support through this enduring process. Anjali's daily excitement about the book put pressure on me to finish, and Evangelina has been patiently hearing me say over and over "the book will be done next month." Much love to both. Now the book is finally done, and hopefully its readers and my colleagues, friends, and family will enjoy it!

Navdeep S. Chandel
August, 2014