Preface

Cancer metabolism as a discipline predates the discovery that genetic mutations are causal drivers for tumor initiation and progression. In the 1920s, Otto Warburg, a pioneering biochemist, first noted that cancer cells preferentially consume glucose and produce lactate even in the presence of ample oxygen—a phenomenon now known as the Warburg effect. As genetics arrived and dominated our understanding of the molecular basis of cancer, interest in metabolism as a potential mechanistic driver of cancer waned. Even so, new diagnostic modalities like FDG-PET reinforced the basic premise of Warburg's work: that tumors display consistent metabolic differences from nonmalignant tissues, and that some of these differences could be exploited in the clinical arena.

Over the past 30 years or so, with the benefit of molecular tools and eventually new technologies in metabolic analysis, researchers have started to focus on why the Warburg effect is so pervasive in cancer cells and seems to provide a growth advantage to tumors. One prevailing theory is that high flow through glycolysis sustains the provision of glycolytic intermediates for anabolic pathways, supporting the synthesis of nucleotides, lipids, and amino acids essential for rapid cell proliferation. However, many recent studies have also positioned the mitochondria as central players in cancer metabolism. Traditionally seen as energy factories (the "powerhouse of the cell," in common parlance), mitochondria are now recognized for their roles in redox balance, in biosynthesis of macromolecules, and as signaling organelles controlling cell fate and function. They provide the necessary energy and building blocks for proliferating cancer cells while generating reactive oxygen species (ROS); these can function to promote oncogenic signaling while also inducing cell death, including ferroptosis.

Cancer cells, therefore, walk a metabolic tightrope, leveraging mitochondrial functions to their advantage while managing death-inducing ROS levels by increasing antioxidant levels to avoid self-destruction. Beyond their roles in biosynthesis and energy production, some metabolites promote tumor initiation and growth through signaling effects that influence gene expression and other activities beyond the traditional metabolic network. "Oncometabolites" like succinate, fumarate, and 2-hydroxyglutarate accumulate as a consequence of cancer-associated mutations in metabolic enzymes and inhibit α-ketoglutarate-dependent dioxygenases, leading to epigenetic changes that drive tumorigenesis.

Modern research has expanded on Warburg's findings, leading to the inescapable conclusion that "cancer metabolism" is far from uniform. Tumors exhibit an incredible degree of metabolic heterogeneity, not just between different types of cancer but sometimes even within different regions of the same tumor. This variability stems from a complex interplay of genetic mutations and environmental factors, producing distinct metabolic phenotypes that evolve as cancer progresses from localized disease that can often be cured by surgery to disseminated and therapeutically intractable metastatic disease. Understanding these shifting metabolic landscapes is crucial for developing targeted therapies.

The tumor microenvironment (TME) presents a unique set of challenges and opportunities for cancer cells. Nutrient availability in the TME is often limited, forcing cancer cells to adapt by activating nutrient-scavenging mechanisms such as autophagy and macropinocytosis. These pathways enable cancer cells to sustain growth under nutrient-deprived conditions and position metabolic adaptation as a mechanism of cancer progression. Interestingly, the metabolic demands and vulnerabilities of noncancerous cells within the TME, including immune cells, can also influence tumor progression.

Advances in our understanding of cancer metabolism have opened new avenues for therapy, particularly in targeting the selective metabolic dependencies of cancer cells. While early attempts at metabolic therapy faced challenges due to toxicity and metabolic plasticity, some modern approaches have been able to capitalize on tumor-specific liabilities. FDA-approved therapies in IDH-mutant leukemias capitalize on the fact that blocking mutant isoforms of these enzymes suppresses oncometabolite production. Moreover, combining metabolic therapies with standard treatments like chemotherapy, radiotherapy, and immunotherapy holds potential for more effective cancer treatment. Chemotherapy and radiotherapy target metabolic pathways and ROS biology, so identifying metabolic enzymes to enhance the efficacy of these therapies holds great promise. Moreover, a significant barrier to immunotherapy is overcoming the exhaustion of CD8 T cells, which have metabolic defects that could be strategically targeted.

The immense scope of metabolic heterogeneity in cancer means that a one-size-fits-all strategy is unlikely to succeed, however. A more personalized approach is necessary, where therapies are tailored to the specific metabolic vulnerabilities of a patient's tumor, particularly given the dynamic nature of cancer metabolism, which can change in response to treatment and disease progression. Diet plays a crucial role in influencing cancer metabolism, further complicating the relationship between nutrition and tumor growth. The future of cancer metabolism research lies in integrating advanced analytical techniques with patient stratification based on genetic mutations and other factors that govern metabolic dependencies. Using metabolomics, metabolic isotope tracers, and imaging technologies to map the metabolic landscape of tumors in real time could lead to the identification of predictive biomarkers and more effective therapeutic strategies.

In this book, a collection of chapters written by pioneers in the field of cancer metabolism highlight modern experiments that have revealed the many complexities of metabolic reprogramming during cancer initiation, progression, and metastasis, and identified opportunities to target these pathways for therapeutic benefit. An important legacy of research in cancer metabolism as highlighted in this book is that the ideas and techniques arising from this discipline have profoundly influenced numerous adjacent fields, including immunology, stem cell biology, and developmental biology. We are grateful to CSHL Press for allowing us to gather a collection of expert contributions and hope this book will be useful to new scientists entering the field. Maybe it will generate a small profit from CSHL Press for us to buy a glass of Bollinger champagne that the three of us can share.

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