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Anne Le *Editor*

The Heterogeneity of Cancer Metabolism

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This book is dedicated to my colleague and mentor, Dr. Edward Gabrielson.

Anne Le

Preface

Genetic alterations in cancer, in addition to being the fundamental drivers of tumorigenesis, can give rise to a variety of metabolic adaptations that allow cancer cells to survive and proliferate in diverse tumor microenvironments. This metabolic flexibility is different from normal cellular metabolic processes and leads to heterogeneity in cancer metabolism within the same cancer type or even within the same tumor.

In this book, the authors delve into the complexity and diversity of cancer metabolism and highlight how understanding the heterogeneity of cancer metabolism is fundamental to the development of effective metabolism-based therapeutic strategies. Deciphering how cancer cells utilize various nutrient resources will enable clinicians and researchers to pair specific chemotherapeutic agents with patients who are most likely to respond with positive outcomes, allowing for more cost-effective and personalized cancer treatment.

This book has three major parts:

Part I: Basic Metabolism of Cancer Cells
Part II: Heterogeneity of Cancer Metabolism
Part III: Relationship between Cancer Cells and Cancer-Associated Fibroblasts

This book is designed for cancer metabolism researchers, cancer biologists, and any other researchers, physicians, epidemiologists, health care professionals of various disciplines, policy makers, and marketing and economic strategists… It is also designed for teaching undergraduate and graduate students and researchers.

The metabolic pathways and their regulations mentioned in this book serve as examples to illustrate the heterogeneity of cancer metabolism and are noninclusive.

Dr. Anne Le is the corresponding author for all the chapters in this book. Email: annele@jhmi.edu.

Baltimore, MD, USA — Anne Le

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About the Editor

Anne Le studied at the Paris Descartes University, Cochin Port-Royal School of Medicine, in France where she obtained a Habilitation degree (https://en.wikipedia.org/wiki/Habilitation), the highest academic qualification a scholar can achieve in Europe. After her clinical training at Henri Poincaré University Hospital, Nancy, in France, she started her postdoctoral research fellowship at the Johns Hopkins University School of Medicine in 2007. Since 2011, Dr. Le has been an independent investigator who has yielded a number of contributions to the field of cancer metabolism, demonstrated by her publication record as a pioneer in the field. She has published in the best journals, such as *Cell Metabolism* and the *Proceedings of the National Academy of Sciences of the United States of America*. Dr. Le has been invited to present her work at several annual American Association for Cancer Research meetings, the most prestigious international meeting for cancer research scientists and professionals, as well as by the National Cancer Institute, and universities in France, Monaco, Japan, and Taiwan. Research media, such as Science Daily, American Association for the Advancement of Science (AAAS), Business Insider, ALN® Magazine, among many others, have written about her work. Dr. Le is highly respected and sought after for her strong proficiency in judging the work and ideas of her peers. She is regularly invited to serve on review panels by prestigious organizations such as the National Institutes of Health and the US Department of Defense. She is frequently asked by highly-cited scientific journals to review manuscripts submitted to their journals.

Part I
Basic Metabolism of Cancer Cells

Glucose Metabolism in Cancer

Sminu Bose and Anne Le

Key Points

- Tumor cells exhibit an upregulation in glycolysis, glycogen metabolism, and gluconeogenesis as opposed to normal cells.
- The metabolic reprogramming underlying the Warburg effect and other changes in glucose metabolism are driven by several oncogenes and tumor suppressors.
- Numerous therapies based on cancer metabolism have been developed but have yet to show success in clinical trials.

Keywords Glucose metabolism · Warburg effect · Glycogenolysis · Gluconeogenesis · Cancer metabolism

Abbreviations

3PO	3-(3-Pyridinyl)-1-(4-pyridinyl)-2-propen-1-one
AGL	Amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase
AKT	Also known as PKB, protein kinase B
ATP	Adenosine triphosphate
CP-320626	5-Chloro-N-[(2S)-3-(4-fluorophenyl)-1-(4-hydroxypiperidin-1-yl)-1-oxopropan-2-yl]-1H-indole-2-carboxamide
F1,6-BP	Fructose-1,6-bisphosphatase
F2,6-BP	Fructose-2,6-bisphosphate
FX-11	3-Dihydroxy-6-methyl-7-phenylmethyl-4-propylnaphthalene-1-carboxylic acid

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G1P	Glucose-1-phosphate
G6P	Glucose-6-phosphate
GBE	1,4-Alpha-glucan branching enzyme
GLUT	Glucose transporter
GSK2	Glycogen synthase kinase 2
GYS1	Glycogen synthase 1
HIF-1α	Hypoxia-inducible factor 1α
HK2	Hexokinase 2
LDHA	Lactate dehydrogenase A
mTOR	Mechanistic target of rapamycin
NAD	Nicotinamide adenine dinucleotide
PCK2	Phosphoenolpyruvate carboxykinase 2
PCK1	Phosphoenolpyruvate carboxykinase 1
PFK	Phosphofructokinase
PFKFB3	6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
PGM	Phosphoglucomutase
PI3K	Phosphoinositide 3-kinase
PPP	Pentose phosphate pathway
PPP1R3C	Protein phosphatase 1 regulatory subunit 3C
TCA	Tricarboxylic acid
TIGAR	TP53-induced glycolysis and apoptosis regulator
TP53	Tumor protein 53
UGP2	UTP:glucose-1-P uridylyltransferase 2
VHL	Von Hippel-Lindau

Introduction

Otto Warburg observed a peculiar phenomenon in 1924, unknowingly laying the foundation for the field of cancer metabolism. While his contemporaries hypothesized that tumor cells derived the energy required for uncontrolled replication from proteolysis and lipolysis, Warburg instead found them to rapidly consume glucose, converting it to lactate [1]. The significance of this finding, later termed the Warburg effect, went unnoticed by the larger scientific community at that time. The field of cancer metabolism lay dormant for almost a century awaiting advances in molecular biology and genetics which would later open the doors to new cancer therapies.