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Introduction to Metabolism

WHAT IS METABOLISM?

IF YOU ASK MY YOUNG DAUGHTER, Anjali, she will tell you that metabolism is about how we break down food and build muscles. At first glance, this is not far from the definition of metabolism, which is a set of pathways to build and break down macromolecules that comprise living matter. These macromolecules include proteins, lipids, nucleic acids (DNA and RNA), and carbohydrates; their biosynthesis is referred to as anabolism. In contrast, these macromolecules can also be broken down into their constituents—amino acids, fatty acids, nucleotides, and sugars—in a process referred to as catabolism. Catabolism can generate energy in the form of ATP and reducing equivalents (NADH, NADPH, and $FADH_2$) to sustain chemical reactions of living organisms (Fig. 1-1). In contrast, anabolic reactions use ATP and reducing equivalents to reassemble products of catabolism. It is astonishing how the basic macromolecules of living matter and the metabolic pathways to generate energy and synthesize cell constituents are highly conserved among organisms. In fact, this profound similarity of basic metabolic pathways across life might be the best evidence for evolution, suggesting that all living organisms evolved from a common source.

WHY STUDY METABOLISM?

Much of biology during the early part of the 20th century focused on elucidating anabolic and catabolic pathways, and, until the 1960s, many Nobel Prize awards in Physiology or Medicine and in Chemistry were given to these metabolism-related discoveries (see Box 1-1). After the discovery of DNA and protein phosphorylation in the mid-20th century, biology entered a new era of understanding gene regulation and signaling pathways. Metabolism was thought to change only as a consequence of changes in signaling pathways and gene expression. In other words, the phenotype of a cell or an organism feeds back on metabolism to acquire the necessary metabolites and energy to function. In the past two decades, however, accumulating evidence suggests that metabolism can actually regulate signaling pathways and gene expression, thereby playing a causal role in dictating divergent biological outcomes, such as

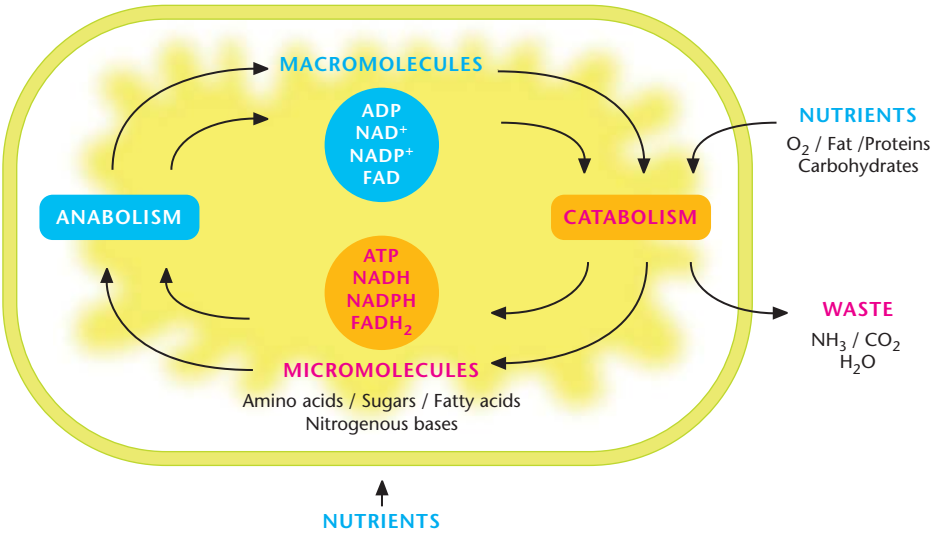

Figure 1-1. Metabolism is the flux through anabolic and catabolic pathways.

cell proliferation, cell death, differentiation, gene expression, and adaptation to stress. Hence, metabolism dictates phenotype. Moreover, an exciting idea is that changes in metabolism underlie diseases such as diabetes, neurodegeneration, cancer, hepatotoxicity, and cardiovascular and inflammatory diseases (Fig. 1-2). The use of widely adopted statins to interfere with cholesterol metabolism to diminish cardiovascular disease is an excellent example of the importance of understanding metabolism to prevent diseases (see Chapter 7). Other widely used medications, such as aspirin, an anti-inflammatory drug, and metformin, an antidiabetic drug, have recently been proposed to target AMP-activated protein kinase (AMPK) and mitochondrial complex I, respectively. It is with great hope that many scientists are testing whether intervening in metabolic pathways could alleviate the suffering caused by these diseases.

An emerging subject is metabolism's connection to signaling and induction of gene expression (see Chapter 10). For example, protein acetylation of lysine residues and protein oxidation of cysteine residues are important regulators of cellular signaling pathways. Acetylation requires acetyl-CoA as a substrate, and protein oxidation requires ROS. Metabolism controls the availability of both acetyl-CoA and ROS. Conversely, signaling pathways regulate metabolism. Notably, the kinase mammalian target of rapamycin (mTOR), which controls growth of cells and organs, as well cancer and the aging process, and thus is a major therapeutic target, exerts its major biological effects, in part, by balancing the anabolic and catabolic pathways within a cell based on nutrient availability. Until the past decade, it was thought that the induction of genes was restricted to regulation by transcription factors. However, in the past two decades, epigenetics has emerged as a powerful mechanism for controlling gene expression, and metabolism plays a role in this. For example,

BOX 1-1. NOTABLE METABOLISM-RELATED NOBEL PRIZES

Year	Name	Citation
Chemistry		
1902	Hermann Emil Fischer	"[for] his work on sugar and purine syntheses"
1907	Eduard Buchner	"for his biochemical researches and his discovery of cell-free fermentation"
1927	Heinrich Otto Wieland	"for his investigations of the constitution of the bile acids and related substances"
1928	Adolf Otto Reinhold Windaus	"for the services rendered through his research into the constitution of the sterols and their connection with the vitamins"
1929	Arthur Harden, Hans Karl August Simon von Euler-Chelpin	"for their investigations on the fermentation of sugar and fermentative enzymes"
1937	Walter Norman Haworth	"for his investigations on carbohydrates and vitamin C"
	Paul Karrer	"for his investigations on carotenoids, flavins and vitamins A and B2"
1938	Richard Kuhn	"for his work on carotenoids and vitamins"
1970	Luis F. Leloir	"for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates"
1978	Peter D. Mitchell	"for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory"
1997	Paul D. Boyer, John E. Walker	"for their elucidation of the enzymatic mechanism underlying the synthesis of ATP"
Physiology or Medicine		
1922	Otto Fritz Meyerhof	"for his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in the muscle"
	Archibald Vivian Hill	"for his discovery relating to the production of heat in the muscle"
1923	Frederick Grant Banting, John James Rickard Macleod	"for the discovery of insulin"
1929	Christiaan Eijkman,	"for his discovery of the antineuritic vitamin"
	Sir Frederick Gowland Hopkins	"for his discovery of the growth-stimulating vitamins"
1931	Otto Heinrich Warburg	"for his discovery of the nature and mode of action of the respiratory enzyme"
1937	Albert Szent-Györgyi von Nagyrapolt	"for his discoveries in connection with the biological combustion processes, with special reference to vitamin C and the catalysis of fumaric acid"
1947	Carl Ferdinand Cori, Gerty Theresa Cori, née Radnitz	"for their discovery of the course of the catalytic conversion of glycogen"
	Bernardo Alberto Houssay	"for his discovery of the part played by the hormone of the anterior pituitary lobe in the metabolism of sugar"

(*Continued*)

BOX 1-1. *(Continued)*

Year	Name	Citation
1953	Sir Hans Adolf Krebs	"for his discovery of the citric acid cycle"
	Fritz Albert Lipmann	"for his discovery of coenzyme A and its importance for intermediary metabolism"
1955	Axel Hugo Theodor Theorell	"for his discoveries concerning the nature and mode of action of oxidation enzymes"
1964	Konrad Bloch, Feodor Lynen	"for their discoveries concerning the mechanism and regulation of the cholesterol and fatty acid metabolism"
1985	Michael S. Brown, Joseph L. Goldstein	"for their discoveries concerning the regulation of cholesterol metabolism"

methylation of histones and DNA requires methyl groups, which are donated by methionine through one-carbon metabolic pathways. Furthermore, the enzymes that cause demethylation are members of the growing α-ketoglutarate-dependent dioxygenase family.

Cancer metabolism has generated a lot of excitement in the past few years (see Chapter 11). In 2008–2009, mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and 2 in several types of malignant gliomas have linked the cancer genetics field to cancer metabolism. Surprisingly, these mutations do not cause major

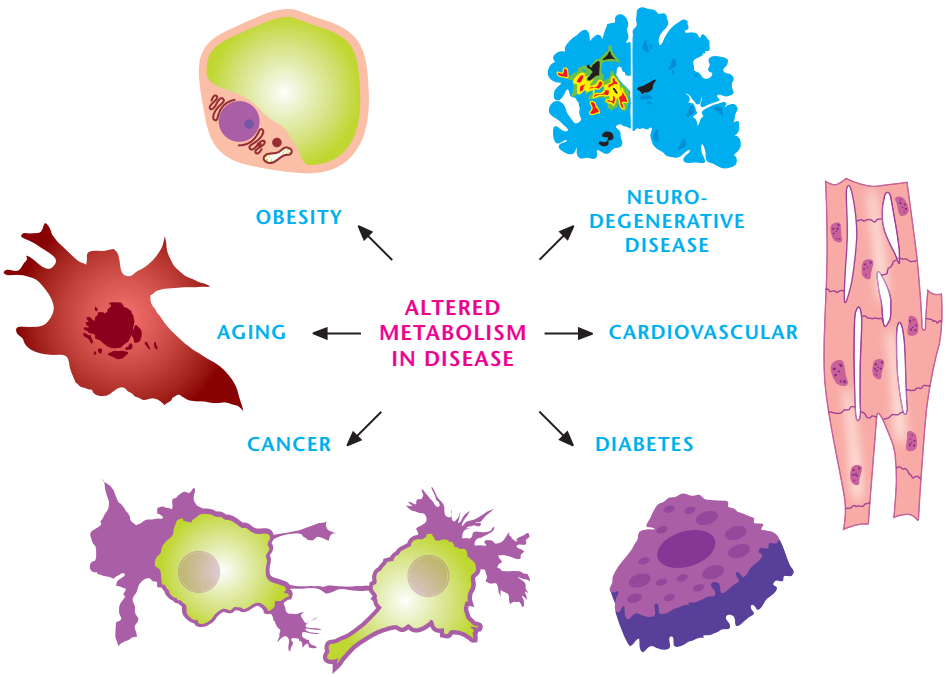

Figure 1-2. Altered metabolism is linked to many common diseases.

changes in metabolic pathways. Instead, the IDH mutations generate a new oncometabolite, 2-hydroxyglutarate (2HG), which regulates epigenetics by inhibiting demethylase enzymes that are members of the α-ketoglutarate-dependent dioxygenase family. Normally, 2HG is detectable at low levels in cells, but shows an increase of >100-fold in tumor samples with IDH mutations. These mutations have now been found to be prevalent in chondrosarcomas and acute myeloid leukemias (AMLs). Remarkably, today there are drugs in clinical trials that can distinguish between wild-type and mutant IDH and are being used for treatment in cancer patients with IDH mutations. Beyond mutations in metabolic enzymes, large-scale functional genetic screens have identified wild-type metabolic enzymes that are necessary for growth of certain types of cancers. Furthermore, large-scale bioinformatic analysis has deciphered a list of wild-type metabolic enzymes that are highly up-regulated across many cancer cells, thus potentially yielding new targets for cancer therapy.

Finally, "textbook" biochemistry has also been invigorated by discovery of new metabolic pathways and metabolic proteins, as well as novel modes of regulating metabolic pathways. For example, pyruvate kinases are one of the major enzymes that regulate glycolysis (see Chapter 3). Yet, the mechanisms by which proliferating cells modulate the activity of pyruvate kinases to control glycolysis to balance their biosynthetic and bioenergetics demand is just being unraveled. Moreover, although it been known for decades that pyruvate is metabolized by mitochondria, it is only recently that the transporter responsible for pyruvate transport into the mitochondria was discovered.

The use of isotope carbon-labeling techniques (see the Appendix) has elucidated interesting new pathways both in vitro and in vivo. For example, the metabolism of the amino acid glutamine through the TCA cycle has been well known for decades. However, in the past few years, through the use of isotope carbon-labeling techniques, it was discovered that glutamine metabolism not only fluxes through the canonical clockwise TCA cycle but also fluxes through a few reverse steps of the TCA cycle. New parameters governing metabolic flux through a pathway are also being revealed using metabolomics and computational modeling. And mitochondria, the central hub of metabolism, have undergone a makeover from being known for decades as the "powerhouse" of the cells to also being appreciated as "signaling organelles" because of their involvement in controlling many divergent biological processes, ranging from cell proliferation to cellular differentiation. The ensuing decades will, no doubt, yield more insight into how metabolism integrates with multiple different biological processes within cells.

HOW SHOULD WE THINK ABOUT METABOLISM?

First, most of us think the importance of metabolic pathways lies in understanding how organisms generate sufficient amounts of energy to conduct biological func-

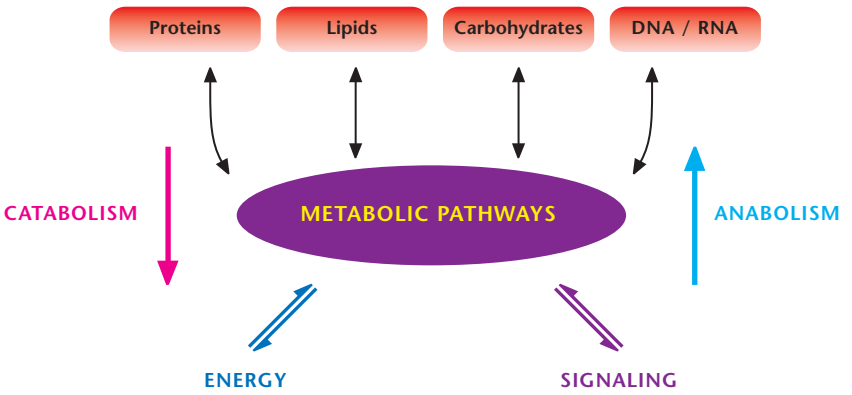

Figure 1-3. Overview of metabolic pathways covered in this book.

tions. However, an equally important function of metabolic pathways is to generate intermediates for biosynthesis of macromolecules (Fig. 1-3). As Hans Krebs, who received the Nobel Prize in Physiology or Medicine in 1953 for his discovery of the citric acid cycle, stated in his Nobel lecture, "Many observations, especially from isotope experiments, support the view that in some micro-organisms the cycle primarily supplies intermediates rather than energy, whilst in the animal and most other organisms it supplies both energy and intermediates." Throughout this book, we will pay attention to both the energy generation and biosynthesis aspects of metabolic pathways. There are illustrative metabolic pathways throughout the book as quick reference guides.

Second, it is essential to always examine why a particular reaction in a metabolic pathway goes in one direction versus another. There is a logic that dictates the directionality and rate of reactions within a given metabolic pathway. Thus, before elucidating metabolic pathways in Chapter 3, essential concepts, such as thermodynamic constraints, enzyme activity, and levels of products versus reactants that are key determinants of directionality and rates of any given reaction within a metabolic pathway, are discussed in Chapter 2. Although new metabolic pathways will be uncovered in the future, they are likely to be constrained by the same parameters outlined in Chapter 2.

Third, it is vital to think consistently about metabolic pathways in the context of biological and physiological functions. Metabolic pathways in cells are continuously responding to diverse stimuli, ranging from growth factors to changes in nutrients, as well as metabolic pathways, and are key decision makers in dictating biological outcomes. It makes sense that, before a cell commits to any biological function, there would be modes of communication to assess whether there is sufficient energy and biosynthetic activity. Throughout the book, metabolic pathways are put in the context of biological and physiological functions.

HOW IS THIS BOOK ORGANIZED?

Navigating Metabolism is not intended to substitute for many of the excellent biochemistry textbooks already available. *Merriam-Webster's Dictionary* defines biochemistry as "chemistry that deals with the chemical compounds and processes occurring in organisms." For many of us, biochemistry looks like static metabolites pinned down in metabolic pathways. Metabolism brings those metabolic pathways to life, because it is about the flux through those pathways and how nutrient availability, genes, and signaling control metabolic pathways. Thus, Chapter 2 begins with parameters that control flux through metabolic pathways, followed by Chapters 3 and 4 on glycolysis and mitochondrial metabolism, the two central carbon metabolic pathways. Chapter 5 explores NADPH, which I refer to as "the forgotten reducing equivalent," as most of us only remember NADH, which is necessary to generate ATP. NADPH is necessary for driving many of the anabolic reactions in our cells. Chapters 6, 7, 8, and 9 describe metabolism relating to sugars, lipids, amino acids, and nucleotides, respectively. These four chapters have similar themes in which I describe the catabolic, anabolic, and signaling pathways for these building blocks. Chapter 10 discusses the cellular signaling pathways that control metabolic pathways. Chapter 11 uses metabolism of proliferating cells as an example to synthesize the concepts presented in the preceding 10 chapters. Finally, Chapter 12, entitled "The Future of Metabolism," is a collection of short essays written by scientists who are currently heavily engaged in investigating cellular metabolism.