Cell Metabolism
Review

The Biology of Cancer: Metabolic Reprogramming Fuels Cell Growth and Proliferation

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Cell proliferation requires nutrients, energy, and biosynthetic activity to duplicate all macromolecular components during each passage through the cell cycle. It is therefore not surprising that metabolic activities in proliferating cells are fundamentally different from those in nonproliferating cells. This review examines the idea that several core fluxes, including aerobic glycolysis, de novo lipid biosynthesis, and glutamine-dependent anaplerosis, form a stereotyped platform supporting proliferation of diverse cell types. We also consider regulation of these fluxes by cellular mediators of signal transduction and gene expression, including the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR system, hypoxia-inducible factor 1 (HIF-1), and Myc, during physiologic cell proliferation and tumorigenesis.

Introduction

In mammals, cell proliferation is required for embryogenesis, growth, proper function of several adult tissues, and tumorigenesis. A primary focus of research on cell proliferation has been understanding the mechanisms that regulate the proliferative state, work that has led to identification of growth-factor signal transduction pathways and transcriptional networks enabling cells to initiate and maintain cell cycling. But the onset of proliferation introduces important problems in cellular metabolism as well, because each passage through the cell cycle yields two daughter cells and requires a doubling of total biomass (proteins, lipids, and nucleic acids). This poses a profound metabolic challenge that must be met if cells are to respond to proliferative stimuli.

Proliferating cells often take up nutrients in excess of bioenergetic needs and shunt metabolites into pathways that support a platform for biosynthesis (Bauer et al., 2004). Signals that stimulate cell proliferation must also participate in the reorganization of metabolic activity that allows quiescent cells to begin to proliferate (Figure 1). Over the past several decades, a consistent picture of intermediary metabolism has emerged from studies on diverse types of proliferating cells. Metabolism in these cells differs from quiescent cell metabolism by high rates of glycolysis, lactate production, and biosynthesis of lipids and other macromolecules (Figure 2). In this review, we focus on the roles of these metabolic activities and the replenishment of intermediates for the tricarboxylic acid (TCA) cycle (anaplerosis) during proliferation. We also discuss current concepts regarding how signal transduction pathways influence cell metabolism.

Most of the work cited below involves proliferating lymphocytes or tumor cells. Lymphocytes and other hematopoietic cells are excellent models for the study of metabolic regulation because quiescent cells can be stimulated to proliferate in vitro and the signaling mechanisms behind cell proliferation are well characterized. Tumor cells are also useful because a wide variety of cell lines are available and the genetic mechanisms leading to tumorigenesis are often known. It should be stressed that "tumor metabolism" is not synonymous with the metabolism of cell proliferation. While proliferation is required for tumors to grow, many factors within the tumor microenvironment can influence cellular metabolism, resulting in heterogeneous metabolic activity. Our interest in tumor cells as discussed here involves the metabolic activities that promote their growth and proliferation.

Proliferating Cells Use Aerobic Glycolysis

In the 1920s, Otto Warburg published the seminal observation that rapidly proliferating ascites tumor cells consume glucose at a surprisingly high rate compared to normal cells and secrete most of the glucose-derived carbon as lactate rather than oxidizing it completely, a phenomenon known as the "Warburg effect" (Warburg, 1925, 1956b). This observation presented a paradox that still has not been completely resolved: Why do proliferating cells, which ostensibly have a great need for ATP, use such a wasteful form of metabolism? Warburg proposed that tumor cells harbor a permanent impairment of oxidative metabolism resulting in a compensatory increase in glycolytic flux (Warburg, 1956a). But later studies on proliferating primary lymphocytes revealed similar patterns, in which more than 90% of glucose carbon was converted to lactate, ruling out the possibility that aerobic glycolysis is unique to tumor cells or that the Warburg effect only develops when oxidative capacity is damaged (Brand, 1985; Hedeskov, 1968; Roos and Loos, 1973; Wang et al., 1976). Indeed, many highly proliferative tumor cell lines that have been carefully studied do not have defects in oxidative metabolism (Moreno-Sanchez et al., 2007).

So why does the Warburg effect occur? Clearly, the high glycolytic rate provides several advantages for proliferating cells. First, it allows cells to use the most abundant extracellular nutrient, glucose, to produce abundant ATP. Although the yield of ATP per glucose consumed is low, if the glycolytic flux is high enough, the percentage of cellular ATP produced from glycolysis can exceed that produced from oxidative phosphorylation (Guppy et al., 1993; Warburg, 1956b). This may be due to the high rate of ATP production during glycolysis compared to

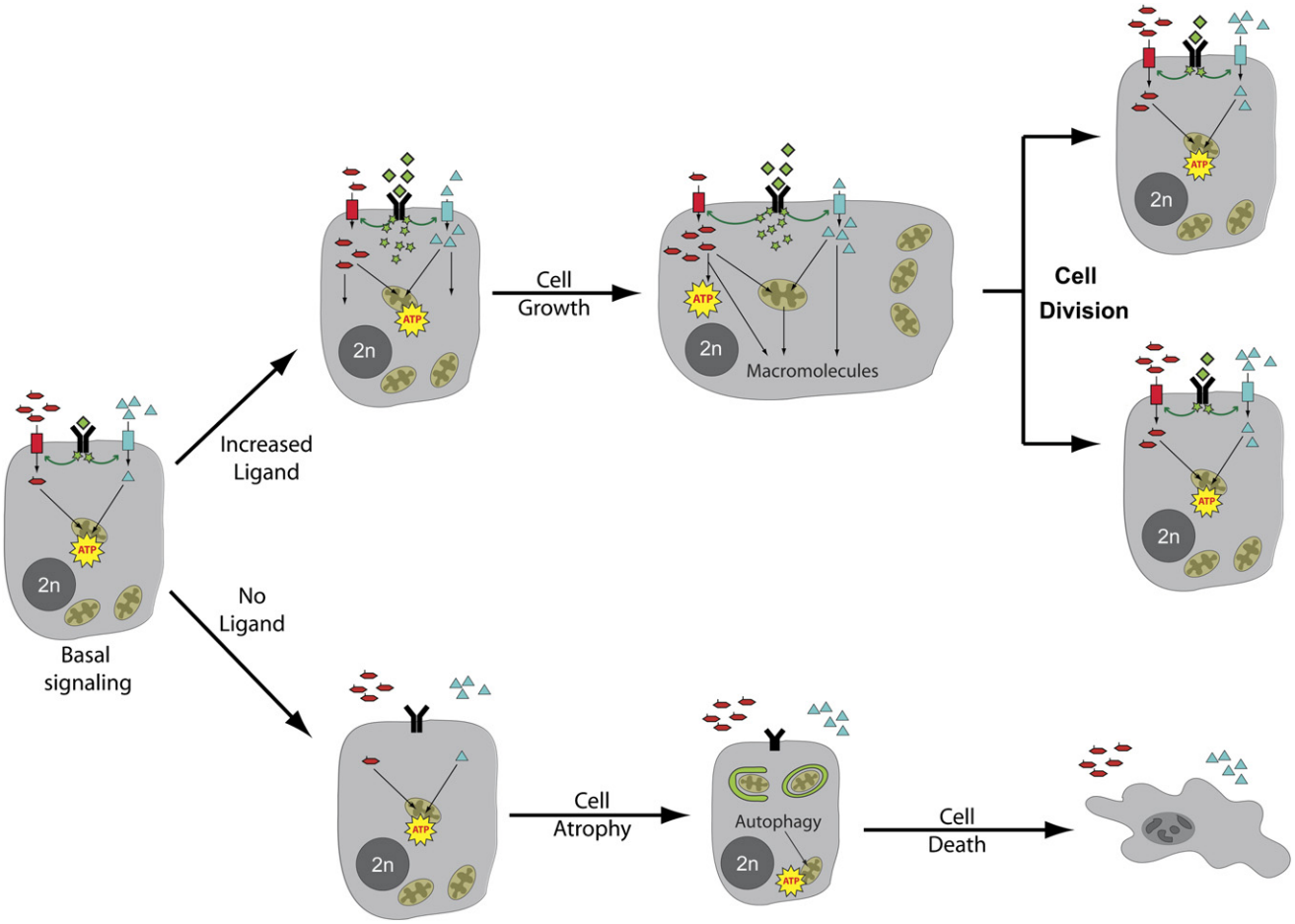

Figure 1. Growth-Factor Signaling Regulates the Uptake and Metabolism of Extracellular Nutrients
At rest, basal levels of lineage-specific growth-factor signaling (green) allow cells to take up sufficient nutrients like glucose (red) and amino acids (blue) in order to provide the low levels of ATP production and macromolecular synthesis needed to maintain cellular homeostasis. In the absence of any extrinsic signals (no ligand), mammalian cells lose surface expression of nutrient transporters. To survive in the absence of the ability to take up extracellular nutrients, growth-factor-deprived cells engage in autophagic degradation of macromolecules and organelles. This is a finite survival strategy, ultimately resulting in cell death. In contrast, increases in ligand signaling instruct cells to begin taking up nutrients at a high rate and to allocate them into metabolic pathways that support production of ATP and macromolecules like proteins, lipids, and nucleic acids. These activities culminate in a net increase in cellular biomass (growth) and, ultimately, the formation of daughter cells.

oxidative phosphorylation (Pfeiffer et al., 2001). Second, glucose degradation provides cells with intermediates needed for biosynthetic pathways, including ribose sugars for nucleotides; glycerol and citrate for lipids; nonessential amino acids; and, through the oxidative pentose phosphate pathway, NADPH. So the Warburg effect benefits both bioenergetics and biosynthesis.

What remains controversial about the Warburg effect is why the rate of lactate production is so high when more of the pyruvate could presumably be oxidized to enhance ATP production. One explanation is simply that glycolysis outpaces the maximal velocity of pyruvate oxidation, so that cells must instead eliminate pyruvate using high-flux mechanisms. Oxidation of pyruvate requires import into the mitochondrial matrix, followed by activity of highly regulated enzymes like the pyruvate dehydrogenase (PDH) complex, whose activity is influenced by phosphorylation, free CoA levels, and the NAD^+/NADH ratio, all of which may limit its activity relative to glycolytic flux. Glycolytic flux may exceed the V_{max} of PDH by more than an order of magnitude during cell proliferation, implying the need for a high-capacity system to avoid accumulation of pyruvate (Curi et al., 1988). In proliferating cells, expression of lactate dehydrogenase A (LDH-A) solves this problem by rapidly consuming pyruvate, regenerating NAD^+ in the face of a relentless glycolytic flux while yielding a product (lactate) that can easily be secreted (Figure 2). LDH-A is induced by oncogenes (c-*myc*, *HER2/neu*, and others) and by mitogen stimulation in lymphocytes, and it participates in xenograft tumorigenicity, implying a prominent role in cell proliferation (Fantin et al., 2006; Marjanovic et al., 1990; Shim et al., 1997).

A further advantage of the high glycolytic rate is that it allows cells to fine tune the control of biosynthetic pathways that use intermediates derived from glucose metabolism. When a high-flux metabolic pathway branches into a lower-flux pathway, the ability to maintain activity of the latter is maximized when flux through the former is highest. In proliferating cells, this has been proposed as a way to resolve the apparent paradox