Chapter 14

ENERGY METABOLISM IN CANCER

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INTRODUCTION

Disruption of the tricarboxylic acid (TCA) cycle in cancer cells can cause various pathological conditions in the human body (1). Cancer cells rapidly consume enormous amounts of glucose to grow and multiply constantly. As a result of this reaction, they produce two ATP molecules and lactic acid. The highly acidic environment created can lead to the death of healthy cells. This energy metabolism is a characteristic feature in all cancer cells, from the early stages of transformation, both in vitro and in vivo, to tumor invasion and metastasis (2, 3). In the literature, this phenomenon, known as the Warburg effect, is observed even in oxygen and intact mitochondria (4, 5). The Warburg phenomenon still needs to be fully resolved. If this uncertainty is resolved, a new treatment target can be determined, and the fight against the disease will become easier.

Mitochondria: Energy Center

Mitochondria have functions on both energy metabolism and cell death in physiological and pathological environments (6). In addition, mitochondria are the organelles where basic reactions such as fatty acid oxidation, gluconeogenesis, proliferation, Ca^{2+} homeostasis, metabolic adaptation, and ketogenesis take place (7). Although it is well known that mitochondria are actively involved in cancer progression, their role in the clinical outcome of cancer patients remains unclear (8, 9). Mitochondria in normal and cancerous cells; consists of three compartments: an inner membrane (IMM), an outer membrane (OMM), and an intermembrane space, and that forms invasions called "crests" from the cell cytosol. The IMM is a gelatinous material containing mitochondrial

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DNA (mtDNA), granules, ribosomes, and ATP synthase particles. It hosts the electron transport chain (ETC) and delimits the matrix of the mitochondria. The TCA cycle takes place in the mitochondrial matrix (9). The OMM enables communication between the mitochondria and the remainder of the cell. OMM is essential for the generation and release of mtROS, cellular stress response, and hypoxia-inducible factors (HIFs), particularly to activate nuclear factor erythroid-derived 2-like 2 (Nrf2) and downstream gene expression factors (10).

Although mitochondrial Ca^{2+} release modifies apoptosis, mitochondrial Ca^{2+} uptake controls mitochondrial metabolism. In this case, Ca^{2+} acts as a bidirectional signaling molecule (9). The increased Ca^{2+} concentration in mitochondria activates several TCA cycling enzymes and stimulates siklik adenozin-3́, 5́-fosfat (cAMP) production. Thus, it increases ATP production by allowing metabolic adaptation (11). However, high Ca^{2+} levels induce the opening of mitochondrial permeability transition pores, trigger cytochrome c release, and initiate apoptosis. As a result, apoptosis occurs. Therefore, Ca^{2+} is also called a signal for programmed cell death (12). In addition to all these, as a result of the decrease in the level of ATP produced by mitochondria, it acts as a signal transmitted to the cytosol in the form of AMP, activating 5'-Adenosine monophosphate-activated protein kinase (AMPK). Thus, anabolic cell functions are replaced by catabolic functions (13).

Energy Regulation Unit: AMPK

It has been reported that the energy production of cancer cells may have switched to glycolytic metabolism due to the insufficiency of angiogenesis that can meet the growing needs of the cells (14, 15). The metabolism change from oxidative phosphorylation (OXPHOS) to anaerobic glycolysis occurs by the induction of genes encoding glycolytic enzymes in response to hypoxia. It occurs due to mutation of HIF-1, mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K)/AKT pathway, and various oncogenes such as tumor protein p53 (p53) and tumor suppressors (16). Enzyme-linked receptors activate the PI3K/AKT/mTOR signaling pathway, which is essential for cell differentiation, proliferation, energy, glucose metabolism, apoptosis, cellular response to oxidative stress, and angiogenesis (17). AMPK regulates various metabolic processes such as mTORC1, p53, and fatty acid synthesis, controlling intracellular energy levels to keep the cell growth rate at an appropriate level (18). Normal cells have some protective mechanisms, such as AMPK, that

can cope with various stresses that cause energy imbalance to maintain their homeostasis (Figure 1) (19). Two impacts of AMPK on energy metabolism are possible. The immediate effect is that under stress conditions like hypoxia, ischemia, and glucose deprivation, AMPK is activated, stimulating fatty acid oxidation to increase ATP production. Through mTOR and p53, AMPK can inhibit glycolysis over an extended period of time. Thus, suppression of AMPK in some cancers may increase glycolysis, contributing to the Warburg effect. AMPK appears to be a metabolic tumor suppressor to maintain cell metabolism and growth at appropriate levels (20). AMPK, a serine/threonine protein complex, consists of 3 significant subunits, a catalytic α-subunit, a skeleton β-subunit, and a regulatory γ-subunit. AMPK is also activated when the cellular level of ATP decreases and the level of adenosine diphosphate/adenosine monophosphate (ADP/AMP) increases, such as during stressful situations in metabolism (21). When AMPK is activated, ATP-depleting cellular events such as protein synthesis or fatty acid synthesis are inhibited, producing stimulatory effects on ATP-generating events, including glucose uptake, glycolysis, and fatty acid oxidation (22). Activation of the α-subunit occurs by AMP and ADP phosphorylation of AMPK. AMP and ADP bind to Thr 172 in the γ-subunit of

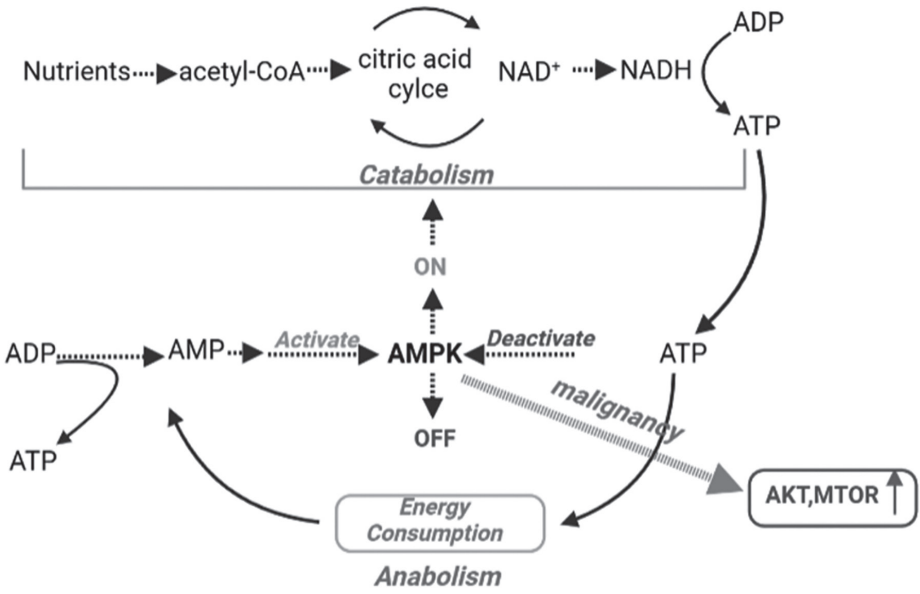

Figure 1 AMP: ATP ratio and AMPK activation and the effects of AMPK activation on metabolism or the effects of AMPK malignancy. Inspired by Shirwany et al.,(22)

AMPK, phosphorylate and activate AMPK (23). In addition, it phosphorylates the α-subunit of AMPK, serine-threonine kinase liver kinase B1 (LKB1), and Ca^{2+}/calmodulin-dependent protein kinase β (CaMKKβ). CaMKKβ is activated by increasing intracellular Ca^{2+} concentration, independent of ATP/ADP/AMP levels (24).

Metabolic Adaptation in Tumors

Metabolic adaptation in tumors goes beyond the Warburg effect. Cancer cells provide redox balances by meeting the energy and macromolecular building block needs of the cells (16). Electron leaks can occur in the ETC during anaerobic glycolysis, resulting in reactive oxygen species (ROS) and other free radicals. Uncontrolled amounts of ROS can harm the body by oxidizing cell macromolecules such as proteins and lipids (25). In a study, they reported that the nicotinamide phosphoribosyltransferase (NAMPT) enzyme of breast cancer cells could block ROS accumulation and delay cell death when glucose is limited by maintaining the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) level. Ultimately, NAMPT can increase the $NADP^+$ pool by supplying NAD^+, leading to improved NADPH production via the induced pentose phosphate pathway (PPP). Normal cells have a relatively low NADPH ratio as they have low resting NADPH consumption; however, due to the high consumption of NADPH in cancer cells, Glucose 6 Phosphate Dehydrogenase Enzyme (G6PDH) enzyme activities are high level. Therefore, excessively increased G6PDH in cancer cells accelerates PPP. PPP is particularly critical for cancer cells because it produces pentose phosphates to ensure high nucleic acid synthesis and provides NADPH, which is essential for both the synthesis of fatty acids and cell survival under stress conditions (26). Thus, cancer cells can overcome glucose deprivation-induced stress using NAMPT (27). Proliferation and DNA synthesis rates in cancer cells largely depend on NAD^+-dependent signaling. Therefore, the conversion rate to NAD^+ is higher in cancer cells than in normal cells (28). In eukaryotes, normally, electrons are transported via NADH. This way, the amount of mitochondrial NAD^+ is reduced, and homeostasis is maintained (29).

mTOR Signals in Cancerous Cells

mTOR is estimated to be active in more than 70% of cancers, leading to tumor growth, metastasis, and angiogenesis (30, 31). mTOR, which has two different

complexes, mTORC1, and mTORC2, is a highly conserved serine/threonine protein kinase. mTOR controls cell growth, proliferation, glucose metabolism, lipid synthesis, mitochondrial function, transcription mechanism, and survival in response to nutritional and hormonal signals (32). The cause of excessive mTOR activation in cancer may be the amplification of components of mTOR complexes, mutations that activate the mTOR pathway, or mutations/loss of mTOR suppressors (33). Therefore, recent research suggests that targeting the mTOR signaling pathway may be an effective strategy for cancer therapy (34).

AMPK can induce autophagy by suppressing the mTOR complex 1 (mTORC1) pathway (19). The mechanism that removes damaged / dysfunctional cellular organelles and proteins in all living cells is called autophagy (35). mTOR inhibitors are the best-understood inducers of autophagy. MTORC1 negatively regulates autophagy by phosphorylating ULK1 (unc-51-like autophagy-activating kinase 1) and TFEB (transcription factor EB) required for autophagosome formation (36). mTORC1 reacts to cellular energy in addition to detecting growth factors.

Cellular energy, growth factors, nucleotides, and stressors all influence mTORC1 activity. The main locations of mTORC1 activation are lysosomes. Growth factors require the brain-enriched Ras homolog (RHEB), a lysosomal GTP-bound Rheb GTPase that interacts with and activates mTORC1 directly (37). Growth factor receptors (EGFR, IGFR) are activated after interacting with insulin-like growth factor (IGF) or epidermal growth factor (EGF). As a result, the PI3K-PDK1-Akt signaling pathway is activated. In addition to detecting growth stimuli, mTORC1 also reacts to cellular energy. The AMP/ATP ratio rises when cellular energy is low, activating the AMPK energy sensor (26, 38). mTORC1 reacts to cellular energy in addition to detecting growth factors. The energy sensor AMPK is activated by insufficient cellular energy, which raises the AMP/ATP ratio (39). Nevertheless, AMPK causes mTORC1 to be downregulated (40).

IGF-IR-Akt axis activation by mTORC2 can control mTORC1, while mTORC1 can inhibit mTORC2. While mTORC2 directly promotes IGF-IR and insulin receptor (InsR), it can also be activated by receptor tyrosine kinases like EGFR and IGF-IR via the PI3K pathway (41-43). AMPK suppresses mTORC1. It then subtly reverses mTORC1's inhibition of mTORC2, causing mTORC2 to become activated (44). Moreover, glutamine deprivation stimulates mTORC2. The rate-limiting enzyme of the hexosamine biosynthesis pathway (HBP),

glutamine:fructose-6-phosphate amidotransferase 1 (GFAT1), is upregulated by activated mTORC2 (45, 46).

DISCUSSION

Cancer continues to be a life-threatening disease that affects a large population worldwide (47). As a result of recent developments, the focus is on the view that cancer is now a 'metabolic disease.' Considering that it is a metabolic disease, inhibition of glycolysis may be the primary target. Yet, the majority of healthy cells in the body also need products from the glycolytic pathway, such pyruvate, to produce energy through OXPHOS (48). It has long been suggested that mitochondria were one of the first organelles of the eukaryotes that evolved from the endosymbiosis of the two prokaryotic cells (49). Thus, it is thought that new organisms (eukaryotes) can survive in the oxygenated world (50). Seyfried et al. reported that non-critical damage in OXPHOS may be one of the findings of mitochondrial dysregulation that can initiate cancer (48). In addition, Davila et al. defined the mitochondrial dysregulation that causes cancer cells to escape from OXPHOS as an evolutionary regression (50). Protection from drugs or therapies that disrupt the glycolytic pathways of normal cells and proper nutrition becomes essential. Ketones, for instance, are a well-known alternative to glucose as an energy source that can shield the brain from dangerous hypoglycemia. A low-carb, high-fat ketogenic diet, when consumed in moderation, can shield the brain from hypoglycemia as well as normal cells from glycolytic inhibition (48, 51, 52).

A cell's metabolism also affects other cells around it. Some cells have been reported to undergo phenotypic changes due to their presence in a growing tumor environment (53). Cancer cells reprogram their microenvironment and maintain their existence through growth factors, cell-cell interactions, and extracellular matrix. As cancer cells proliferate, the composition of the extracellular environment changes due to the high utilization of glucose and glutamine, and lactate accumulation occurs (38, 54). The increase in lactate level decreases monocyte migration and dendritic cells and T cells activation and so promotes disease (55).

It has been reported that glycolysis is increased by transcriptional upregulation of AKT, mTOR, HIFs, glucose transporters, and glycolytic enzymes, which causes tumor survival and growth (56). mTORC1 has emerged

as a central node for nutrient sensing and a coordinator of increased anabolic (lipid and nucleotide synthesis) activities in proliferating cells (57). Cancer cells hyperactivation of MYC and mTORC1 may create metabolic vulnerability (58). This critical information may provide unique therapeutic interventions in reducing cancer cell proliferation and survival compared to non-malignant cells (56). As an energy regulator, AMPK maintains cellular energy balance and regulates mitochondrial biogenesis (19). AMPK has been extensively used therapeutically to treat a variety of metabolic diseases, including diabetes. In lung and ovarian malignancies, AMPK has been found to decrease tumor growth (59, 60). As AMPK has been demonstrated to play tumor-suppressive functions, a number of small compounds that activate AMPK have been examined in preclinical cancer models. For example, canagliflozin, a diabetes drug that activates AMPK, has been shown to inhibit cell proliferation, survival, and tumorigenicity of prostate and lung cancer cells (19, 61). Although numerous AMPK agonists have anti-tumor effects in preclinical animals, it is not known if AMPK activation results in tumor suppression. Because AMPK can have tumor-promoting function in some tumor settings, therapeutic treatments against AMPK may very well be taken into consideration. If a tumor settles without impairing the LKB1-AMPK pathway, AMPK can help sustain the survival of tumor cells by protecting them from metabolic stress. Reexpression of LKB1 was discovered to prevent glucose starvation-induced cell death in lung adenocarcinoma cells by protecting NADPH because AMPK inhibits the synthesis of fatty acids. Therefore, it may also protect against oxidative stress that glucose deprivation can cause (62).

CONCLUSION

Certain cancer types cannot be stopped from progressing with current medical treatments. Cancerous cells need a lot of energy, accelerating the disease's development and spread. However, if the energy metabolism in cancer cells can be controlled, cancer metastasis can be prevented, and the disease healing. It is clear from the information above that several approaches are being used to address the energy metabolism of cancer. Hence, profound research on energy regulatory mechanisms, target pathways, or oncogenes in cancer cell metabolism is required to unravel the metabolic mystery of cancer.

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