

Nutrient Metabolisms in Cancer and Related Signaling Pathways

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Abstract. Metabolic reprogramming is recognized as an essential hallmark in carcinogenesis. By investigating the cancer-specific alterations in metabolism, several common cancer phenotypes, such as accumulated somatic mutations due to gene instability, irregular nutrient consumption, uncontrolled growth and proliferation, and aberrational mitochondrial activities, becomes the interest of study. In this article, the overall profile of cancer metabolic activities including glucose and glutamine metabolism, macromolecules synthesis, aerobic glycolysis, pentose phosphate pathways, and mitochondrial activity, as well as two important signaling pathways (PI3K/AKT/mTOR and p53) regarding cancer metabolism are discussed. During cancer progression, the proto-oncogenes are amplified, and the tumor suppressor genes are repressed due to gene instability when cancer over-proliferated. The epigenetic changes affecting cellular signaling pathways and then triggering alterations in biosynthesis and bioenergetics to support cancer growth and proliferation with sufficient building blocks and energy. The article aims to give an overview of those cancer-associated metabolisms and show a profile of cancer-related metabolites and mutated enzymes. It also highlights the interconnections between metabolic activities, the interactions between signaling pathways and cancerous metabolism, and oncometabolites and aberrational enzymes that could potentially promote carcinogenesis; hence, become therapeutic targets for treatments.

Keywords: Cancer Metabolism, Mitochondria, Signaling Pathway.

1. Introduction

In the past decades, there are promising development of technological applications, such as chromatography and histopathology, to identify metabolites and macromolecules (including enzymes and transcription factors) for discovering potential therapeutic targets and understanding their underlying pathways. Those studies allow us to have a better understanding of cancer metabolism and associated signaling pathways. Other than the mutual understanding of cancerous phenotypes such as over proliferation, genetic instability, invulnerability to apoptosis, and motility, other phenotypes and genotypes of cancer cells are not always convergent. In the perspective of cancer progression, cancer cells seem to change their genotypes as they form a benign tumor to malignant tumor, then metastasis [1]. And likely due to the different stress acted on the cancer cells from the macroenvironment, cancer cells located in different regions of the body show different phenotypes, even though they originate from the same tumor [1]. Moreover, different cancer types may possess different phenotypes. The phenotypes reflected on the mitochondrial activities are not universal, which is addressed later in the article. The benign tumors suppress mitochondrial respiration, while the malignant tumors acquire intensive mitochondria activities of oxidative phosphorylation, which contradicts the Warburg theory in 1920s [2]. Hence, this article is to analyze cancer metabolism from the perspective of biosynthesis and bioenergetics, which is fundamental and mutual in all stages of carcinogenesis.

2. Deregulated Uptake of Nutrients Accumulation

2.1. Glucose Metabolism

Glucose is a primary energetic substrate. The carbohydrates, triacylglycerols, and proteins can ultimately be broken down to glucose through gluconeogenesis, when glucose is scarce. Glucose can only be transported by glucose transporters, due to its high molecular weight. In quiescent cells, the glucose uptake is dependent on the growth factors (e.g., insulin). To upregulate the glucose consumption in cancer cells, the oncogenic mutations on PI3K signaling pathway could induce the activity of glucose transporters then to increase the glucose influx. The activation of PI3K signaling pathway can also promote hexokinase (or glucokinase if it is in the liver) to phosphorylate glucose converting glucose to glucose-6-phosphate, as shown in Figure 1. The glucose phosphorylation can instigate glycolysis generating energy in downstream metabolism. In parallel with glycolysis, glucose can also fuel the ribose synthesis (as its form of ribose-5-phosphate), branched from glucose-6-phosphate through pentose phosphate pathway (PPP). Ribose is an important building block for protein and DNA synthesis. Furthermore, PPP is also a major pathway producing nicotinamide adenine dinucleotide phosphate (NADPH), which is a strong reducing agent that can be used in maintaining cellular redox hemostasis and as a reducing equivalent for fatty acid synthesis.

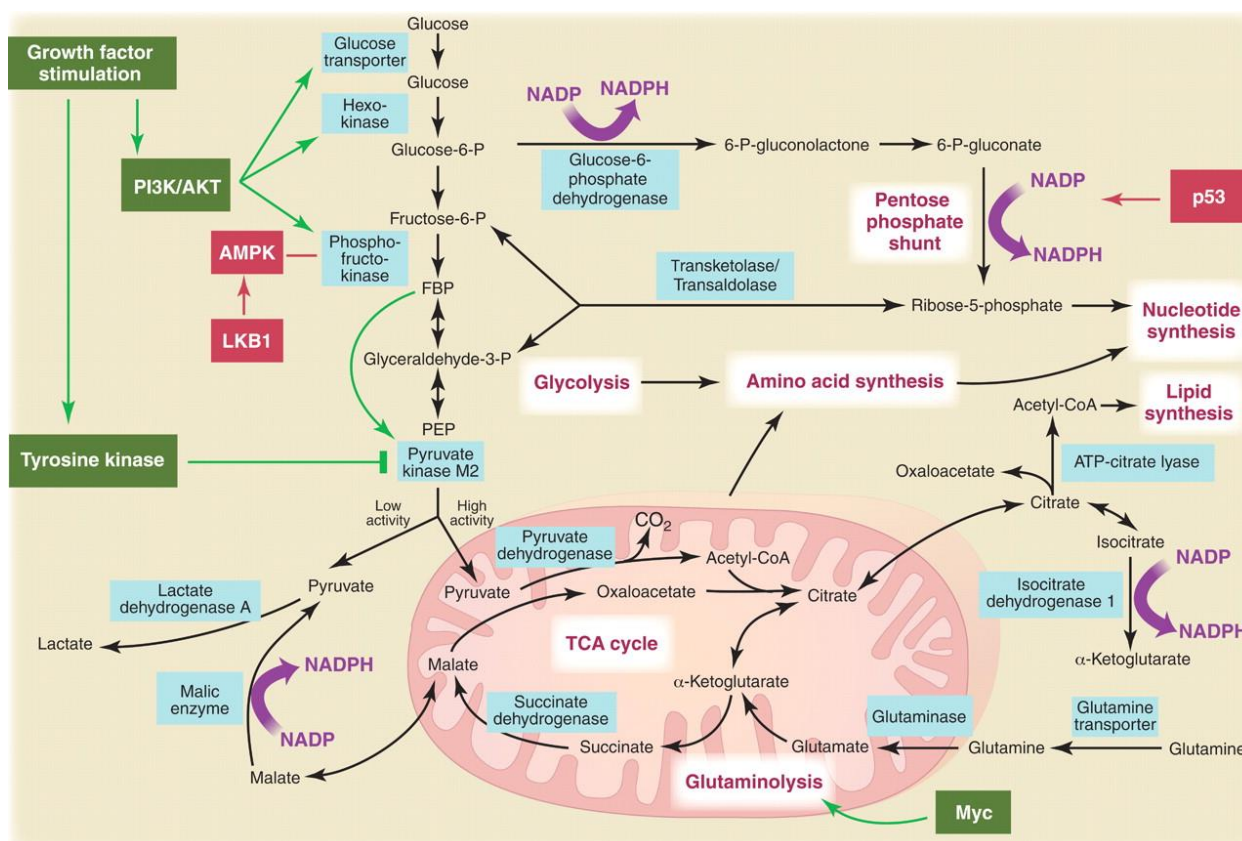


Figure 1. Metabolic pathway of glucose and glutamine [3]

If glucose undergoes glycolysis producing pyruvate as an end product, pyruvate can either come across mitochondria membrane for adenosine triphosphate (ATP) synthesis, or act on lactate dehydrogenase generating lactate in cytosol. In quiescent cells, pyruvate undergoes oxidative phosphorylation (OXPHOS) producing ATPs in the present of sufficient oxygen. While glycolysis is enhanced to make up the imbalance ATP/ADP ratio, only if OXPHOS is insufficient under hypoxia [4]. However, in cancer cells, glycolysis and OXPHOS are two competitive metabolic pathways. The glycolysis and OXPHOS pathways in cancer cells are discussed in the later section. Overall, deregulated glucose uptake is highly exhibited in cancer cells, for glucose can be used for biosynthesis and bioenergetics to satisfy cancer cells' anabolic needs for proliferation. Thus, this provides a

diagnostic opportunity for cancer positron emission tomography (PET) imaging. By using radioactive pharmaceuticals to bind with glucose, 2-deoxy-2-[18F] fluoroglucose (FDG) can be used to highlight the regions with high consumption of glucose [5]. This technology is used to examine premalignant lesions or tumors. Integration of PET and computed tomography (CT) can provide more accurate and graphic results especially for non-FDG-sensitive as well as malignant cancer types [5].

2.2. Glutamine Metabolism

Glutamine is utilized as a nitrogen and carbon donor for biosynthesis. And the glutamine metabolic intermediates participate in Krebs cycle for bioenergetics. Especially in kidney, glutamine metabolism contributes to balancing redox homeostasis.

In glutamine metabolism, amino acid glutamine can be converted to glutamate by glutaminase in mitochondria or by transamination with keto acids found in Krebs cycle. Transamination allows glutamine to provide critical nitrogen sources for making other essential amino acids; it also provides carbon sources for gaining a variety of non-essential amino acids [2]. Glutamate acts on glutamate dehydrogenase to form α -ketoglutarate and generate NADPH in mitochondria (Figure 1). The excessive α -ketoglutarate could enter Krebs cycle and promote the Krebs cycle intermediate, malate, to cross the mitochondria membrane and generate NADPH in cytosol (Figure 1). Moreover, glutamine could also produce glutathione, which involved in detoxification of oxidants [6]. Even though the radicals that are generated from the electron transport chain (ETC) can instigate the signaling pathway of reactive oxygen species (ROS), which promote tumorigenesis, the excessive ROS could disturb the macromolecule synthesis and create cellular stress in cancer cells [7]. Failure to maintain the redox hemostasis can lead to cell apoptosis. The delicate balance of ROS level has been found in majority of cancer cells, which both of ROS and antioxidants concentrations are elevated [7]. The synthesized NADPH and glutathione can neutralize the free radicals and maintain redox homeostasis. Thus, it is found that the glutamine uptake in cancer cells is faster than that in quiescent cells [8]. However, by exploiting the feature of glutamine metabolism, research also shows that the increase in glutamine consumption during chemotherapy and radiotherapy can induce the glutathione generation; hence, lessen treatments' side effects [6].

Furthermore, The RAS pathway can accelerate the scavenge of extracellular proteins, and the proteins are recycled back to amino acids including glutamine by protein catabolism. The proto-oncoprotein c-Myc upregulates the glutamine transporters and glutaminase [2]. The inhibition of first step of glutamine metabolism, glutaminase, gives an antitumor effect, as reported in various glutamine-sensitive cancer types such as breast cancer and glioblastoma [2, 9]. Using stable isotope labeling, labelled glutamine (^{18}F -4-fluoroglutamine) allows diagnosis of cancers in certain areas, where organs are heavily consuming glucose, such as brain [6].

3. Biosynthesis, Bioenergetics and Redox Homeostasis

3.1. Glycolysis

In 1920s, Warburg observed that the cancer cells prefer glycolysis despite the availability of adequate oxygen levels, which is proven to be true in certain cancer types. From the perspective of energy generation, in anaerobic condition, only 2 (mol/mol glucose) ATPs are generated, and lactate are produced and secreted as extracellular content. In the aerobic condition, 36 (mol/mol glucose) ATPs are provided by electron transport chain (ETC) where oxidative phosphorylation (OXPHOS) takes place. Even though it seems that ATPs produced through pyruvate fermentation route are much less than what are generated in OXPHOS route, which contradict the prediction that cancer cells tend to acquire more energy for survival and proliferation. Further studies indicate several reasons explaining this metabolic change from OXPHOS to aerobic glycolysis.

Firstly, during cell's biosynthesis, ATP is moderately needed compared to quiescent cells. Instead, macromolecules, such as fatty acid, are more important for cell's proliferation. Redirecting glycolytic intermediates to pentose phosphate pathway can give ribose-5-phosphate and NADPHs, which can

be utilized for fatty acid, nucleotides, and protein synthesis. Secondly, in cancer metabolism, anabolic demands should be fulfilled to satisfy the cancer proliferative capacity. The exponential growth from one abnormal cell to more than 10^9 cells require sufficient truncated Krebs cycle intermediates (citrate) and glycolytic intermediates. Moreover, if glucose is committed to ATP production alone, the rising concentration of ATP in the cells can inhibit the activity of the enzymes that are responsible for glycolysis and Krebs cycle, which is unfavorable to macromolecule synthesis [3].

Furthermore, lactate, as a byproduct of aerobic glycolysis, is converted from pyruvate by lactate dehydrogenase and excreted out by monocarboxylate transporters (MCTs). MCTs can transport lactate in and out of cellular membrane. The transportation depends on extra- and intracellular pH gradient. But the concentration differences are not only affected by lactate, but acetate, pyruvate, butyrate, and ketone bodies in the cells and macroenvironment [10]. What's more, lactate can shuttle to neighboring quiescent cells, creating tumor-favored environment. When lactate is acidified in the tumor's macroenvironment, the lactic acid triggers the inflammatory response, so that the macrophages secrete cytokines and growth factors that promotes tumorigenesis and carcinogenesis [10]. Targeting MCTs and lactate dehydrogenase by applying inhibitors or genetic knockdown could create therapeutic vulnerabilities for cancer treatments [11].

3.2. Pentose Phosphate Pathway

In quiescent cells, the release of growth factors, activates signaling pathway PI3K/AKT/mTOR, which extracellularly stimulates glucose transporters, hexokinase, and phosphofructokinase to increase glucose uptake rate, promote glycolysis, and generate more glycolytic intermediates that are glucose-6-phosphate (G6P), fructose-6-phosphate (F6P), glyceraldehyde-3-phosphate (G3P), as shown in Figure 1. And those glycolytic intermediates can be further utilized in pentose phosphate pathway (PPP). If the cells are in need of proliferation, growth factors induce tyrosine kinase to negatively regulate pyruvate kinase M2 lowering the generation of pyruvate and redirecting glycolytic intermediates to PPP (Figure 1).

PPP is a crucial source for NADPH generation, which is a powerful reducing agent for biosynthesis and balancing redox homeostasis. And the production of R5P can act as an essential building block for DNA, protein, energy carriers (ATP, NAD^+ , FAD), and CoA synthesis. PPP satisfies the cell's anabolic proliferation demand, which is found to have elevated activity in malignant cancer types [12]. PPP can switch between oxidative phase and non-oxidative phase based on the cell's need. In the oxidative phase, ribose-5-phosphate (R5P) can be synthesized by G6P on glucose-6-phosphate dehydrogenase (G6PD), which also generate NADPH as byproduct. In the nonoxidative phase, R5P is generated from F6P and G3P on transketolase (TKT) and trans aldolase (TALDO) (Figure 2). Since the reactions acted on TKT and TALDO are reversible, R5P can also be broken down and converted back to F6P and G3P. By controlling the enzymes participating in PPP, the cells can adjust the generation of NADPH and R5P. However, the p53 pathway could downregulate the expression of G6PD, inhibiting the downstream production of NADPH and R5P [12].

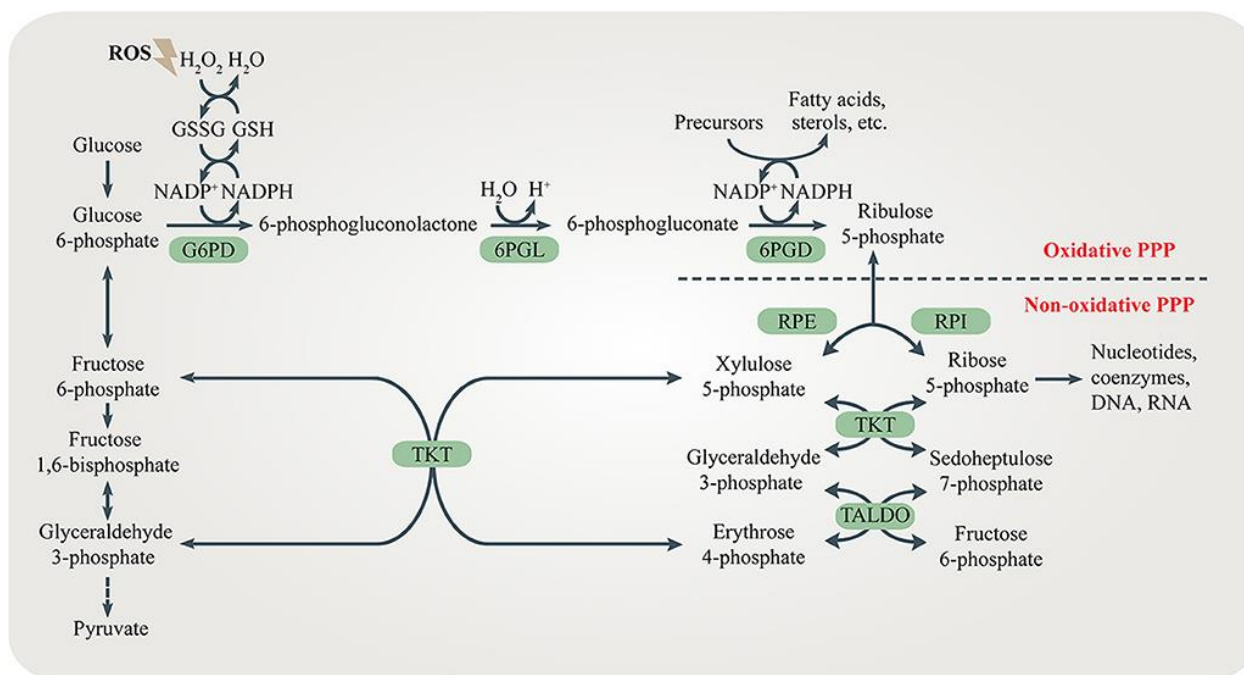


Figure 2. Pentose phosphate pathway [13]

3.3. Mitochondria Activity

Mitochondria is the powerhouse to supply bioenergetics. The Krebs cycle, that uses pyruvate from glycolysis, as well as β -oxidation, that uses saturated long chain fatty acid CoA from lipolysis, are to generate high energy electron carrier NADH and FADH_2 . While electrons from NADH and FADH_2 are passed onto the protein complexes and the enzymes located on the mitochondria matrix, the protons H^+ are pumped out to the intermembrane space. The concentration gradient of H^+ drives oxidative phosphorylation (OXPHOS) converting ADP to ATP.

Keto acids, the intermediates from the Krebs cycle, are essential ingredients for making amino acids from transamination in the cytosol. Both keto acids, malate and citrate, can be released through the mitochondria membrane to the cytosol (Figure 1). Malate reacts on malic enzyme producing pyruvate and NADPH, or it can act on malate dehydrogenase to produce oxaloacetate then phosphoenolpyruvate, which supports gluconeogenesis. Citrate can be broken down to oxaloacetate and acetyl-CoA by citrate lyase. Oxaloacetate can either convert to malate producing NADPH or continue the route of gluconeogenesis if the glucose is low in the bloodstream. Free acetyl-CoA in the cytosol is an important precursor for fatty acid synthesis. Moreover, citrate can react on aconitase forming isocitrate in cytosol, also producing NADPH through isocitrate dehydrogenase.

Furthermore, glutamate generated from glutamine metabolism goes through oxidative deamination in mitochondria located in the liver cells, producing NADPH and α -ketoglutarate, which is an important source for NADPH synthesis in the human body. The excessive α -ketoglutarate enter Krebs cycle promoting generation of malate, resulting more NADPH synthesis by Malic enzyme.

Mutations on enzymes functioning in the Krebs cycle within the mitochondria would cause tumorigenesis. The loss-of-function mutation on α -ketoglutarate dehydrogenase would fail to convert α -ketoglutarate to succinyl CoA in the Krebs cycle. The remaining α -ketoglutarate is then converted to 2-hydroxylglutarate, which is the competitive inhibitor of enzyme histone demethylase [14]. The inhibition of histone demethylase causes uncontrolled gene expression, which is found in gliomas [14]. Moreover, the mutation on succinate dehydrogenase can cause stromal tumor and kidney cancer [14]. Also, the deficiency in enzyme fumarase can lead to leiomyoma, which is commonly found in uterine smooth muscle or kidney [14].

With the continued study of aerobic glycolysis in cancer cells, it is not universal for all cancer types that the glycolytic ATP generation always majorly fuels the cancer cells. ATP generation from glycolysis could occupy as high as 64% of energy generation or as low as 0.31% energy generation

leaving the rest of ATP generated from OXPHOS in mitochondria [15]. Thus, not all cancer types share the feature of aerobic glycolysis. Furthermore, research on mitochondria in cancer cells proves that mitochondria is not completely dysfunctional by oncogenic mutation, contradicting Warburg's theory. But it's observed in several cancer types that the suppression of mitochondria respiration is caused by RAS signaling pathway or high level of glucose present in the blood [15, 16].

Recent discoveries suggest that the mitochondria metabolism could be a promising target for cancer treatment. It is found that the oncocytoomas, a benign tumor, accumulates defect mitochondria. The glycolytic phenotype in oncocytoomas suggests that the limited function of mitochondria gives less energy production and biosynthesis as well as cause other profound cellular dysfunctions [2]. Thus, the tumor is limited to benign stage. On contract, the malignant tumors, such as oncolytic renal Birt-Hogg-Dube tumor, accumulate functional mitochondria [2]. Thus, the role of mitochondria played in tumorigenesis is more than what meets the eyes.

4. Signaling Pathways

4.1. PI3K/AKT Signaling Pathway

In carcinogenesis, for the cluster of cancer cells to evolve from benign tumor to malignant tumor and eventually achieve metastasis, it would need to acquire phenotypes of over proliferation, genetic instability, invulnerability to apoptosis, and motility. Among those phenotypes, the over proliferative potential is primary and essential that acquired by every cancer type. The cancer cells exploit the function of PI3K (phosphoinositide 3-kinase) pathway by oncogenic mutations. Type I PI3K is mostly related to human cancer, for PI3K pathway can induce lipid and nucleotide synthesis as well as down-regulate cell autophagy [17, 18]. It is also responsible for gene translation control. Together with signaling pathway RAS/RAF/MEK/ERK, which controls transcription of proliferative mRNAs in nuclei, the activation of PI3K signaling pathway can remove the blockade on the proliferative mRNAs to allow their translation.

The heterodimers type IA PI3K contain a regulatory subunit and a catalytic subunit (p110). The regulatory subunits p85 α , p55 α , p50 α are encoded from gene PIK3R; p85 β from gene PIK3R2; and p55 δ from gene PIK3R3. Isomeric catalytic subunits (p110 α , p110 β , p110 δ , p110 γ) are encoded from genes PIK3CA, PIK3CB, PIK3CG, PIK3CD respectively. Different mutations on PIK3R2 multiple sites give cancer cells insulin resistance [17]. Failure to respond to growth factor insulin can give cell unlimited glucose intake. Moreover, multiple mutations in gene PIK3CA are mostly discovered in cancer cells, as PIK3CA play important roles in cell proliferation, growth factor signaling, and oncogene transformation [17].

Extracellular ligands bind to receptor tyrosine kinase (RTKs), cytokine receptors, integrins, and G-protein-coupled receptors (GPCRs) [19]. The phosphorylated tyrosine residues on the ligand receptors can bind with the regulatory subunit of type I PI3K and activate its catalytic subunit, whereas GPCRs can activate G protein on the membrane allowing PI3K activation. The catalytic subunit of PI3K then phosphorylates PI (4, 5) P2 (phosphatidylinositol-4,5-bisphosphate) into PI(3, 4, 5)P3 (phosphatidylinositol-3,4,5-triphosphate) and signals downstream proteins (Figure 3). PTEN (phosphatase tensin homolog) enzyme is always active in the normal cells, and it can cleave the phosphate group from PIP3 and converted back to PIP2. If PTEN is inhibited by loss-of-function mutation, PI3K pathway will be activated all the time. Mutations in PTEN is widely observed in different tumor types [17]. PDK-1 (phosphoinositide dependent kinase 1) binds to one of PIP3, and the AKT protein binds to another adjacent PIP3 through the PH (pleckstrin homology) domain. The AKT isomeric proteins are activated by the phosphorylation from PDK-1 and free mTOR2 (mammalian target of rapamycin complex 2) in the cytosol. The phosphorylated AKT isoforms (AKT1, AKT2, and Akt3) can initiate streams of subsequent reactions relating to cell survival and cell growth.

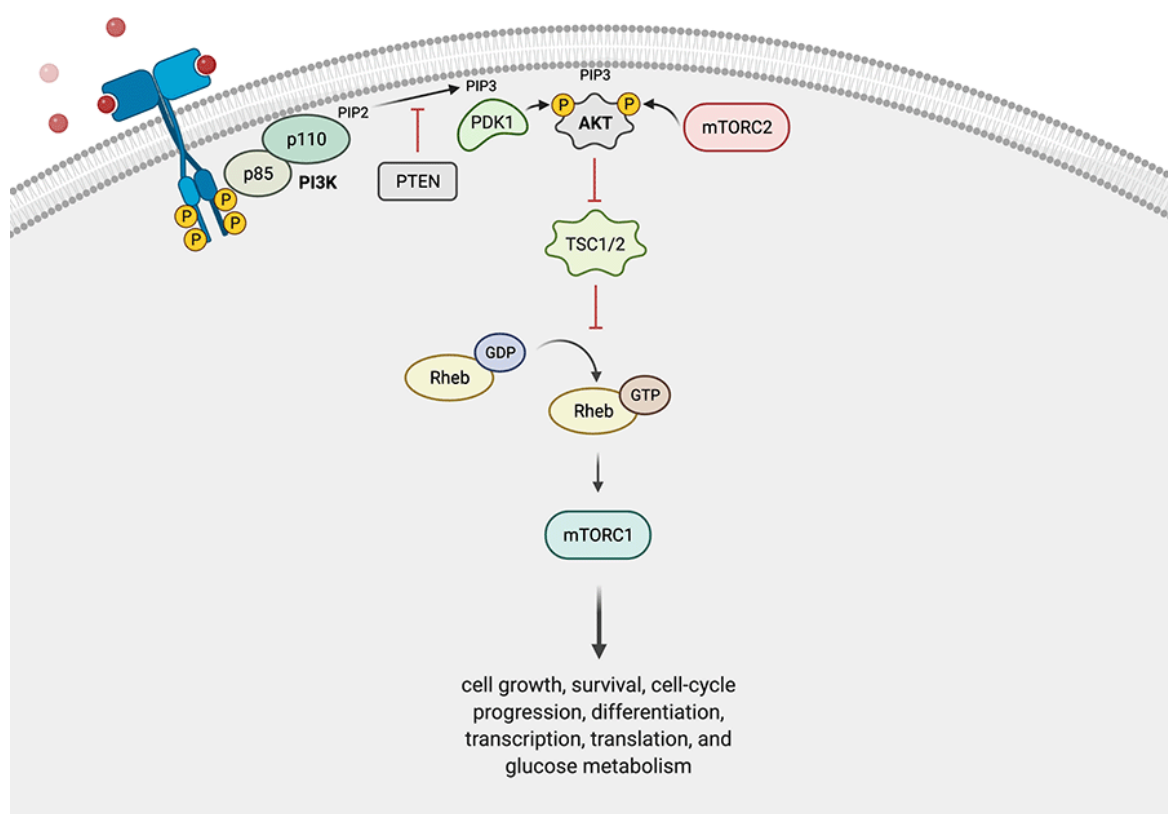


Figure 3. PI3K signaling pathway [20]

AKT can promote cell survival by avoiding cell autophagy. AKT can directly phosphorylate FOXO transcription factor, where its phosphorylation prevents the expression of their tumor suppressor gene [19]. Furthermore, it also can support cell growth by inducing glucose metabolism, nucleotide synthesis, and lipid synthesis. AKT protein directly phosphorylate proteins participated in glycolysis and support non-oxidative pentose phosphate pathway making ribose [19]. It also activates ATP-citrate lyase. The activation of ATP-citrate lyase can increase the citrate, which travels out of mitochondria and breaks down into acetyl-CoA and oxaloacetate, facilitating lipid production. The increased lipid production is found in melanoma, breast cancer, and lung cancer, for lipid production allows the tumor cells to alter its membrane composition for resistance of oxidative stress [8].

Rheb GTPases can activate mTOR1 (mammalian target of rapamycin complex 1). The active monomer Rheb protein (Rheb-GTP) can be inhibited and converted back to Rheb-GDP by TSC (tuberous sclerosis complex). Since TSC is constituted by TSC1 and TSC2 protein, AKT and ERK (from RAS pathway) can cause TSC to decouple allowing accumulation of Rheb-GTP (Figure 3). As one of important PI3K/AKT pathway downstream effector, mTORC1 upregulates the macro-nutrients uptake, such as extracellular proteins. The recovery of proteins can undergo protein catabolism, if under the deprivation of amino acids [8]. What's more, mTORC1 stimulates flux through glycolysis and pentose phosphate pathway in oxidative phase [19]. The generated NADPH through oxidative pentose phosphate pathway can be used to release the oxidative stress that caused by cancer cells over-proliferation. By activating mTOR1, S6 kinase can be phosphorylated and work on S6 protein located on ribosomes, so that the gene translation can be activated. Furthermore, certain mRNAs (elf4E-sensitive mRNAs) require elongation factor 4E (elf4E) to translate into proteins (e.g., cyclins) that are necessary for cell division [21]. mTOR1 could phosphorylate and cleave 4EBP (elf 4E binding protein), which is bonded to elf4E as a blockage preventing mRNA translation.

4.2. p53 Signaling Pathway

When the cells under the exposure of cellular stresses and DNA damage, the tumor suppressor protein p53, as a transcription factor, recruits' coactivators to remodel DNA, exposing core promotor

on the gene. And it binds with promoters and induce RNA polymerase transcription. The p53 protein triggers growth arrest, DNA repair, senescence, and apoptosis, which are the phenotypes that cancer cells acquire for their survival, proliferation, and metastasis [22]. The oncogenic alterations in gene TP53 cause the inactivation of p53 protein, which found in malignant cancers developed in breast, lung, liver, and skin [22]. Failure to initiate DNA repair process gives cell genic instability. With the ability of irregular cell growth and over proliferation, the accumulation of gene mutations causes the cells eventually transform into cancerous cells.

The p53 protein can be regulated by post-translational modification (PTMs). One of the most studied PTMs is phosphorylation by MDM2. Its binding on serine 15 (Ser 15) amino acid site can down-regulate the activity of p53. Thus, the overexpression of regulatory protein MDM2 can deactivate p53 pathway. However, the phosphorylation of on Ser 15 site by ATR protein kinase can prevent the coupling with MDM2. Phosphorylation on different serine residues of p53 protein is dependent on the level of DNA damage and cellular stress [22]. Moreover, the acetylation on different lysine residues can promote the activity and stability of p53, which is critical for cancer treatments [22].

The restoration of p53 protein's function is critical for cancer treatment (Figure 4). Loss-of-function mutations on p53 DNA binding domain are majorly observed in those oncogenic aberrations, and several small molecules and peptides are discovered for repairing the function by protein truncation, protein-protein interactions, protein-peptide interaction, and PTMs [23]. Those manipulations are tested in preclinical mouse trials, showing inhibition of tumor growth. Another approach is to target the p53 regulator, MDM2. The development of p53-MDM2 complex antagonists mimics the binding ability of p53 protein; those small molecules can bind with overexpressed MDM2, maintaining p53's activity and functions in tumor cells [23]. More research and clinical trials are needed for further therapeutic development, but the research proves that restoration of p53 function in tumor cells can improve the traditional radio- and chemotherapy [23].

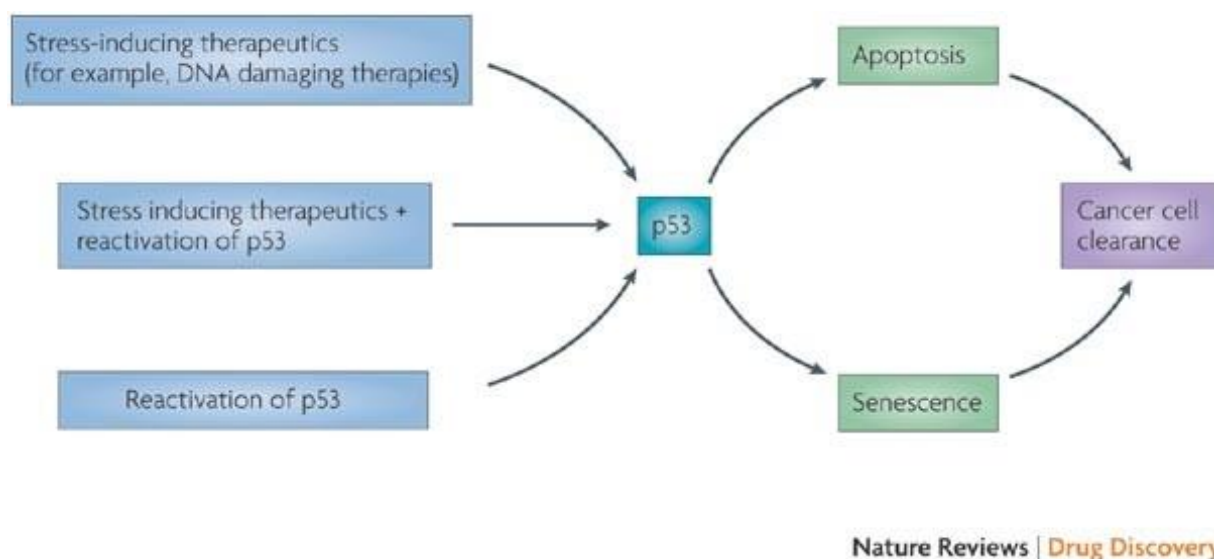


Figure 4. P53 signaling pathway [23]

5. Conclusions

Undoubtably, the different phenotypes are observed as cancer cells progress or undergo adaptation of different macroenvironments. Those epigenetic changes are due to accumulation of gene mutations from over proliferation. However, the biosynthesis and bioenergetics of cancer cells always depend on the nutrient metabolism and are regulated by signaling pathways. The consumption of nutrients including glucose and glutamine can serve as targets of cancer scanning. Metabolic intermediates from glycolysis and Krebs cycle can fuels biosynthesis and maintains redox hemostasis in cancer cells. Mitochondria play a crucial role for bioenergetics, and their ability of respiration is associated

with carcinogenesis. The mutated enzymes in mitochondria could also potentially promote tumorigenesis. Oncogenic signaling pathway PI3K and tumor suppressive signaling pathway p53 regulate the metabolism and trigger downstream cascade. Either amplifications or mutations on the signaling pathways could greatly affect cancer cells growth and survival. By discovering cross-link between nutrient metabolism, metabolic intermediates, and signaling pathways, it could shed a light to understand how cancer cells can adapt to cellular stress as they proliferate, develop resistance to drugs, support their over proliferative potential. Moreover, by exploiting the cancer metabolism, new therapeutic targets and vulnerabilities can be discovered for cancer diagnosis and cancer treatment.

References

- [1] Faubert B., Solmonson A., DeBerardinis R. J. Metabolic reprogramming and cancer progression [J]. SCIENCE, 2020, 368 (6487): 152-+.
- [2] Wallace D. C. Mitochondria and cancer [J]. NATURE REVIEWS CANCER, 2012, 12 (10): 685 - 98.
- [3] Heiden M. G. V., Cantley L. C., Thompson C. B. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation [J]. SCIENCE, 2009, 324 (5930): 1029 - 33.
- [4] Zheng J. Energy metabolism of cancer: Glycolysis versus oxidative phosphorylation (Review) [J]. ONCOLOGY LETTERS, 2012, 4 (6): 1151 - 7.
- [5] Griffeth L. K. Use of PET/CT scanning in cancer patients: technical and practical considerations [J]. Proc (Bayl Univ Med Cent), 2005, 18 (4): 321 - 30.
- [6] Altman B. J., Stine Z. E., Dang C. V. From Krebs to clinic: glutamine metabolism to cancer therapy [J]. NATURE REVIEWS CANCER, 2016, 16 (10): 619 - 34.
- [7] Liou G. Y., Storz P. Reactive oxygen species in cancer [J]. FREE RADICAL RESEARCH, 2010, 44 (5): 479 - 96.
- [8] Pavlova N. N., Thompson C. B. The Emerging Hallmarks of Cancer Metabolism [J]. CELL METABOLISM, 2016, 23(1): 27-47.
- [9] Gross M. I., Demo S. D., Dennison J. B., et al. Antitumor Activity of the Glutaminase Inhibitor CB-839 in Triple-Negative Breast Cancer [J]. MOLECULAR CANCER THERAPEUTICS, 2014, 13 (4): 890 - 901.
- [10] Doherty J. R., Cleveland J. L. Targeting lactate metabolism for cancer therapeutics [J]. JOURNAL OF CLINICAL INVESTIGATION, 2013, 123 (9): 3685 - 92.
- [11] Fantin V. R., St-Pierre J., Leder P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance [J]. CANCER CELL, 2006, 9 (6): 425 - 34.
- [12] Jin L., Zhou Y. Crucial role of the pentose phosphate pathway in malignant tumors [J]. Oncol Lett, 2019, 17 (5): 4213 - 21.
- [13] Ge Tongxin, Yang Jiawen, Zhou Shihui, et al. The Role of the Pentose Phosphate Pathway in Diabetes and Cancer [J]. Frontiers in Endocrinology, 2020, 11.
- [14] Morin A., Letouze E., Gimenez-Roqueplo A. P., et al. Oncometabolites-driven tumorigenesis: From genetics to targeted therapy [J]. INTERNATIONAL JOURNAL OF CANCER, 2014, 135 (10): 2237 - 48.
- [15] Potter M., Newport E., Morten K. J. The Warburg effect: 80 years on [J]. BIOCHEMICAL SOCIETY TRANSACTIONS, 2016, 44: 1499 - 505.
- [16] Chiaradonna F., Gaglio D., Metallo C. M., et al. Oncogenic K-ras decouples glucose and glutamine metabolism to support cancer cell growth [J]. FEBS JOURNAL, 2011, 278: 199-.
- [17] Goncalves M. D., Hopkins B. D., Cantley L. C. Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer [J]. NEW ENGLAND JOURNAL OF MEDICINE, 2018, 379 (21): 2052 - 62.
- [18] Janku F., Yap T. A., Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? [J]. NATURE REVIEWS CLINICAL ONCOLOGY, 2018, 15 (5): 273 - 91.
- [19] Hoxhaj G., Manning B. D. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism [J]. NATURE REVIEWS CANCER, 2020, 20 (2): 74 - 88.

- [20] Castel Pau, Toska Eneda, Zumsteg Zachary S., et al. Rationale-based therapeutic combinations with PI3K inhibitors in cancer treatment [J]. *Molecular & Cellular Oncology*, 2014, 1 (3): e963447.
- [21] Saxton R. A., Sabatini D. M. mTOR Signaling in Growth, Metabolism, and Disease [J]. *CELL*, 2017, 168 (6): 960 - 76.
- [22] Marei H. E., Althani A., Afifi N., et al. p53 signaling in cancer progression and therapy [J]. *CANCER CELL INTERNATIONAL*, 2021, 21 (1).
- [23] Vazquez Alexei, Bond Elisabeth E., Levine Arnold J., et al. The genetics of the p53 pathway, apoptosis and cancer therapy [J]. *Nature Reviews Drug Discovery*, 2008, 7 (12): 979 - 87.