METABOLIC CHANGES IN CANCER CELLS AND THE WARBURG EFFECT

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Abstract. *Background: Cancer cells maintain their growth and viability through metabolic changes. One of their main features is the Warburg effect, i.e., their preference for glycolysis over oxidative phosphorylation for energy production, even when oxygen is sufficient. This phenomenon is associated with oncogene activation, inactivation of tumor suppressor genes, hypoxia-inducible factors, and other factors.*

Keywords: *Cancer metabolism, Warburg effect, aerobic glycolysis, HIF-1α, MYC, PI3K/AKT/mTOR pathway, mitochondrial dysfunction, glycolysis inhibitors, metabolic therapy.*

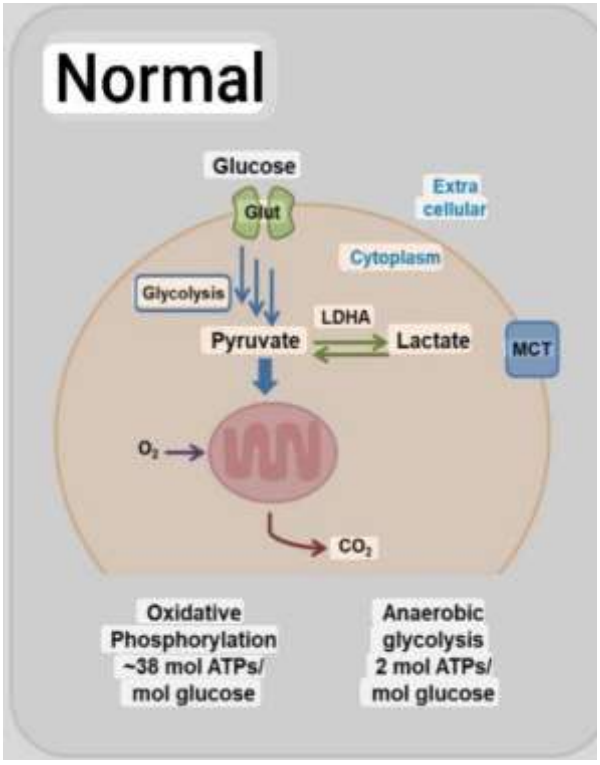
Introduction

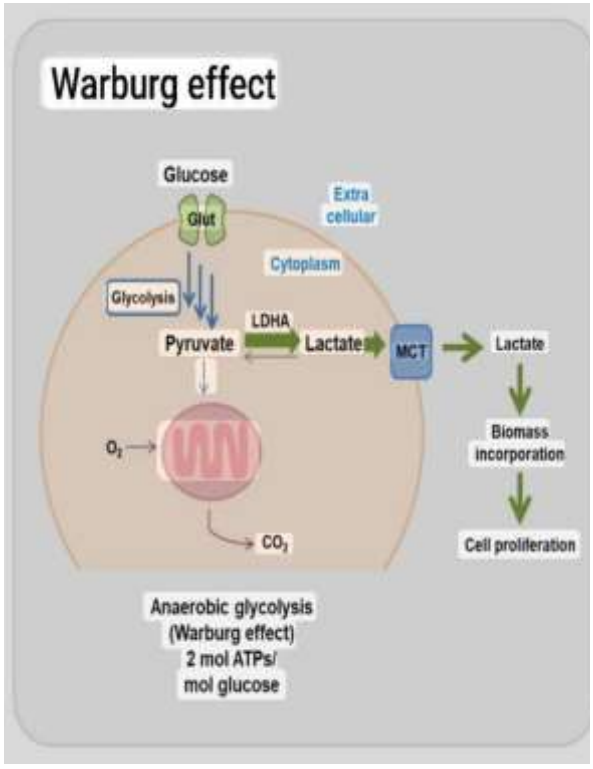
Cancer is one of the most pressing global health challenges, affecting millions of lives each year. One of the unique characteristics of cancer cells is their metabolic reprogramming, i.e., their reliance on completely different mechanisms than normal cells for energy production and survival. One of the most important of these metabolic changes is the Warburg effect, in which cancer cells prefer glycolysis over oxidative phosphorylation as their primary energy source, even when oxygen is available.

Discovered in the 1920s by the German biochemist Otto Warburg, this phenomenon has long been considered a key problem in cancer pathogenesis. Initial hypotheses suggested that the Warburg effect was due to mitochondrial dysfunction in cancer cells, but subsequent studies have shown that this process is associated with oncogene activation, inactivation of tumor suppressor genes, hypoxia-inducible factors, and disruption of signaling pathways. This article reviews the molecular basis of the Warburg effect, metabolic plasticity, energy supply of cancer cells, and therapeutic strategies. Glycolysis inhibitors targeting the Warburg effect, drugs that stimulate mitochondrial metabolism, and the prospects for combination therapy are discussed. The results of the study are expected to provide an important scientific basis for a deeper understanding of cancer metabolism and the development of new therapeutic approaches.

Main part

Metabolic changes in cancer cells and the Warburg effect 1.1. The specificity of cancer metabolism Cancer cells reprogram their metabolic processes to grow and maintain their viability. Normal cells mainly use the mitochondrial oxidative phosphorylation (OXPHOS) pathway for energy production, because this process allows for the maximum production of ATP from glucose. Cancer cells, on the other hand, produce energy through aerobic glycolysis, which is known as the Warburg effect. If the maximum energy is obtained from glucose during the oxidative phosphorylation (OXPHOS) process, why do cancer cells use aerobic glycolysis (Warburg effect)? The reason why cancer cells use the Warburg effect (anaerobic glycolysis) is not only to obtain maximum energy, but also to meet a number of other biological and metabolic needs. Yes, oxidative phosphorylation produces maximum energy (more ATP), but for cancer cells, these processes may be less useful, taking into account other factors. Let us consider in more detail the reasons for these processes:





1.Rapid energy supply for rapid growth and division. Cancer cells are forced to grow and divide rapidly, which requires a high rate of energy and building blocks. In oxidative phosphorylation, all of the glucose is used to produce ATP via the Krebs cycle and the electron transport chain. These processes are relatively slow and require more oxygen. Through the Warburg effect, cells rapidly convert glucose into pyruvate, producing rapid

energy, and also into other metabolic intermediates, such as lipids and nucleic acids, in addition to energy production. This provides the materials needed for rapid growth. 2. Oxygen deficiency (hypoxia) and oxidative stress. Cancerous tissues are often in a state of hypoxia (lack of oxygen). Since oxidative phosphorylation requires oxygen, this process cannot function efficiently due to a lack of oxygen. The Warburg effect does not require oxygen, so cancer cells can continue to produce energy even in hypoxia. In addition, during oxidative phosphorylation, reactive oxygen species (ROS) are formed along with the flow of electrons in the electron transport chain, which can damage cells. The Warburg effect reduces the formation of ROS. 3. The need for metabolic intermediates. The Warburg effect ensures not only energy production, but also the production of metabolic building blocks. From pyruvate and other intermediates formed during glycolysis, cancer cells can produce essential building blocks such as lipids, proteins, and nucleic acids. The increase in these substances is very important for rapidly growing cells. 4. Rapid response and adaptation. Anaerobic glycolysis, also known as the Warburg effect, allows cells to adapt quickly. If a cell needs energy quickly, it can quickly convert glucose to pyruvate under anaerobic conditions. For oxidative phosphorylation, the previous steps (glucose to pyruvate, pyruvate to acetyl-CoA) and other processes require more time and energy. The Warburg effect allows for the production of more ATP in a short time. 5. Metabolic stability. Cancer cells rapidly change their metabolism, and they activate various metabolic pathways to adapt to these changes. The Warburg effect helps the cell maintain metabolic stability, because this process does not depend on oxygen conditions. Oxidative phosphorylation works effectively only in the presence of oxygen, which is sometimes not beneficial to cancer cells. 6. Water and ion exchange The Warburg effect also plays an important role in metabolic hydration (water and ion exchange). During the anaerobic phase of glycolysis, the cell produces more lactate. Increased lactate can create an acidic environment, which in addition to cancer cells, helps to ensure cell growth and metastasis. 1.2. Warburg effect in different cancers. The Warburg effect is observed in almost all types of cancer, but it can manifest itself differently in different tumors. These differences are related to the cell type, genetic changes, and microatrophy of the cancer. The following are the specific features of the Warburg effect in different types of cancer:. 1. Breast cancer. The Warburg effect is stronger in HER2-positive and triple-negative (TNBC) types. Glucose consumption increases due to high expression of GLUT1 and HK2. Lactate production increases, affecting surrounding fibroblasts and immune cells. The PI3K/AKT/mTOR signaling pathway is activated, accelerating metabolism. 2. Lung cancer (NSCLC and SCLC). In NSCLC (non-small cell lung cancer), KRAS mutation induces the Warburg effect. SCLC (small cell lung cancer) is characterized by very high glucose consumption. PD-L1 expression is high, and lactate reduces the

activity of immune cells. 3. Brain tumors (Glioblastoma – GBM) Glioblastoma is very aggressive and relies mainly on aerobic glycolysis. HIF-1α is activated, which breaks down glucose even under hypoxic conditions. Lactate transport by MCT4 creates an immunosuppressive environment around glioma. Due to the activity of the enzyme PKM2, metabolism adapts to biosynthetic needs. 4. Stomach and intestinal cancer In colorectal cancer, MYC and PI3K/AKT pathways enhance the Warburg effect. Lactate production metabolically reprograms surrounding fibroblasts, which supports tumor growth. High glucose consumption in gastroesophageal cancers is observed in PET-CT diagnostics. 5. Blood cancers (Leukemia, Lymphoma, Myeloma). In acute myeloid leukemia (AML), glycolysis prevails over mitochondrial metabolism. Lactate production reduces the ability of the immune system to attack. In B-cell lymphomas, glucose metabolism is activated through the mTOR and MYC pathways. 6. Liver cancer (Hepatocellular carcinoma - HCC). GLUT1 and LDH-A are highly expressed, which leads to rapid breakdown of glucose. HIF-1α and MYC signaling pathways are activated, allowing the tumor to adapt. Liver cancer releases lactate into the environment and activates fibroblasts, which provide additional nutrients to the tumor. 7. Kidney cancer. In clear-cell renal cell carcinoma (ccRCC), a mutation in the VHL gene activates the Warburg effect. The conversion of glucose to lactate leads to a decrease in mitochondrial activity in these tumors. In PET-CT diagnostics, high glucose consumption of colon cancer is clearly visible due to the Warburg effect. 1.3. The main causes of metabolic changes in cancer cells include: Oncogene activation and inactivation of tumor suppressor genes; High expression of glycolytic enzymes; Altered mitochondrial function; Activation of hypoxia-inducible factors (HIF-1α); These processes contribute to the rapid proliferation of cancer cells, their escape from apoptosis, stimulation of angiogenesis, and their hiding from the immune system. **2.** Molecular basis of the Warburg effect The Warburg effect is regulated by several important signaling pathways: 2.1. HIF-1α and hypoxia-inducible mechanisms HIF-1α (Hypoxia-Inducible Factor 1-alpha) is a transcription factor that plays an important role in the response of cells to oxygen deficiency (hypoxia). It plays a central role in changing the metabolism of cancer cells, especially in processes associated with the Warburg effect. 1. What is HIF-1α and its structure HIF-1α is the main component of the HIF-1 transcription factor complex. This complex consists of two parts: HIF-1α - is activated in the absence of oxygen. HIF-1β - is constantly expressed and binds to HIF-1α, forming an active complex. Under normoxic (oxygen-sufficient) conditions, HIF-1α is rapidly degraded, but under hypoxic conditions it is stabilized and shows its ability to affect gene expression. 2. Regulation of HIF-1α The activity of HIF-1α is mainly regulated by oxygen levels and proline hydroxylase enzymes

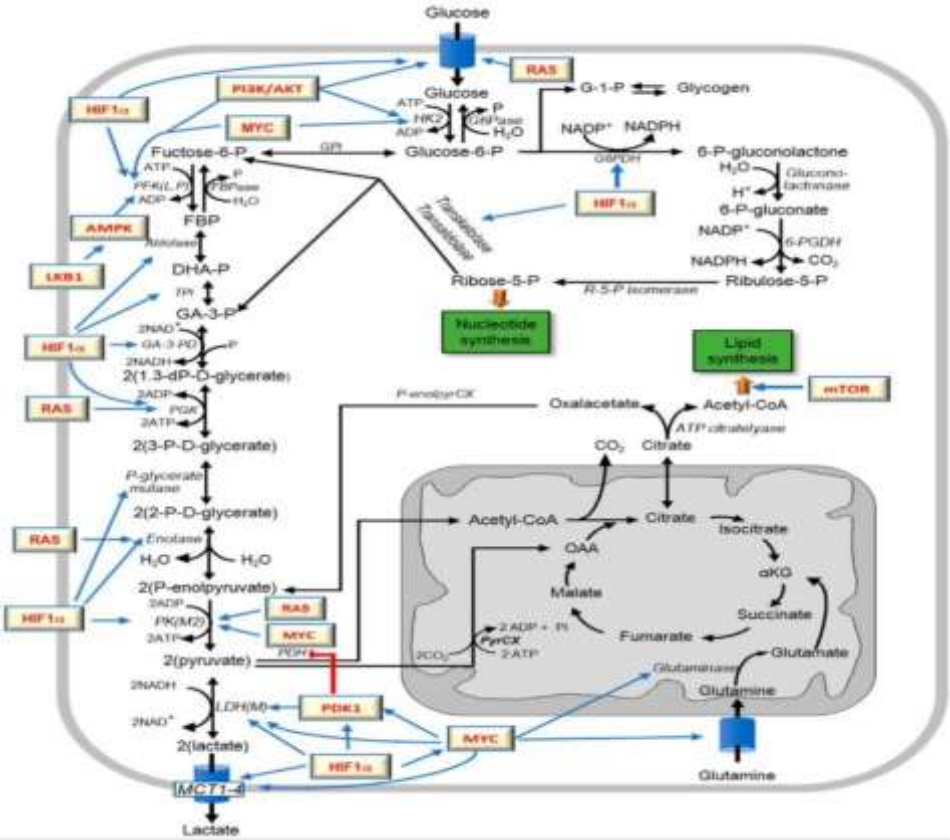
(PHD). Under normoxic conditions (when oxygen is sufficient), proline hydroxylases (PHD) hydroxylate proline residues of HIF-1α.

As a result of this process, the von Hippel-Lindau (VHL) protein degrades HIF-1α through the ubiquitin-proteasome system. As a result, HIF-1α cannot be activated and hypoxia-related genes are not expressed. Under hypoxic conditions (oxygen deficiency), PHD enzymes cannot function in the absence of oxygen, so HIF-1α is protected from degradation. HIF-1α enters the cell nucleus and binds to HIF-1β. This complex binds to DNA sites called HREs (Hypoxia-Response Elements) and activates hypoxia-responsive genes. 3. The role of HIF-1α in cancer cells HIF-1α plays an important role in cancer development because it: Increases glycolysis - activates enzymes such as GLUT1 (glucose transporter) and PFK (phosphofructokinase). Increases lactate production - LDHA (Lactate Dehydrogenase A) is activated, resulting in a further increase in the Warburg effect. Stimulates angiogenesis – increases the expression of VEGF (Vascular Endothelial Growth Factor), which creates new blood vessels for cancer cells. Promotes cancer cell survival – stimulates alternative pathways for ATP production, keeping cells active even in conditions of oxygen deprivation. Numerous studies have shown that high levels of HIF-1α are associated with various types of cancer, including breast, lung, liver and brain tumors. 4. Therapeutic strategies related to HIF-1α Since high activity of HIF-1α ensures the survival of cancer cells, new methods for cancer therapy are being developed by targeting it. Therapeutic strategies based on blocking HIF-1α: HIF-1α inhibitors(YC-1, PX-478) – These drugs reduce the transcriptional activity of HIF-1α. Glycolysis inhibitors (2-deoxyglucose) – Reduce the effect of HIF-1α by stopping glucose metabolism. VEGF antagonists (Bevacizumab) – Inhibit angiogenesis and limit the growth of cancer cells. 5. The relationship between HIF-1α and the Warburg effect HIF-1α and the Warburg effect are closely related: HIF-1α activates glycolytic enzymes, helping cancer cells produce energy through the Warburg effect. HIF-1α suppresses mitochondrial respiration, adapting cells to anaerobic metabolism. As a result of these processes, cancer cells continue to grow without depending on oxygen. 2.2. MYC Oncogene and Metabolic Reprogramming MYC Oncogene and Metabolic Reprogramming MYC is an oncogene that regulates cell growth, proliferation, and metabolism and is highly expressed in many types of cancer. MYC mutations or overexpression increase the energy demand of cancer cells, causing their metabolic changes (metabolic reprogramming). 1. MYC Oncogene What is it? MYC is a transcription factor that activates many metabolic pathways within the cell. This oncogene has isoforms such as MYC, L-MYC, and N-MYC. The main functions of MYC: Accelerate cell proliferation Increase ribosomal RNA and protein synthesis Adapt to the metabolic needs of the cell Suppress apoptosis c-MYC plays a key role in cancer development and

regulates the metabolism of glucose, amino acids, fatty acids, and nucleotides. 2. MYC and Metabolic Reprogramming. Cancer cells require more energy and biosynthetic substrates to grow and divide than normal cells. The MYC oncogene controls this process through the following pathways: A) Glucose Metabolism and the Warburg Effect. MYC increases the expression of GLUT1 (glucose transporter), helping the cell to take up more glucose. It activates the enzymes HK2 (Hexokinase 2) and PKM2 (Pyruvate kinase M2), accelerating the glycolysis process. Cells rely on glycolysis instead of mitochondrial respiration, which enhances the Warburg effect B) Mitochondrial Biogenesis and Patterning. MYC can increase mitochondrial number through PGC-1α (mitochondrial biogenesis regulator). At the same time, MYC ensures that cancer cells are not dependent on oxygen by suppressing mitochondrial respiration. C) Nucleotide Biosynthesis and DNA Synthesis Cells need to produce nucleotides for rapid division. MYC activates the pentose phosphate pathway (PPP), which promotes nucleotide synthesis. Activation of ribonucleotide reductase (RNR) is controlled by MYC, which accelerates DNA synthesis. D) Amino Acid Metabolism MYC activates glutaminolysis, which promotes the use of glutamine as a primary fuel. Glutamine and other amino acids enter the cell via the SLC1A5 and SLC7A5 transporters. Glutamine is converted to alpha-ketoglutarate, which enters the TCA cycle and provides ATP production. E) Fatty Acid Synthesis MYC activates ACLY (ATP-citrate lyase) and FASN (fatty acid synthase), which increases membrane synthesis and energy storage. 3. Role of MYC in Cancer MYC overexpression is found in many types of cancer: Breast cancer – MYC overexpression accelerates cell proliferation. Lung cancer – MYC suppresses mitochondrial activity and prioritizes glycolysis. Neuroblastoma – Amplification of the N-MYC gene plays an important role in this type of cancer. Colorectal cancer – MYC alters the metabolic needs of cells and promotes their growth. 4. Targeting MYC: Therapeutic Approaches High levels of MYC ensure the survival of cancer cells. Therefore, blocking MYC is an important strategy in oncotherapy. MYC activity can be reduced in the following ways: A) Suppression of MYC transcription BET inhibitor (JQ1) – inhibits MYC mRNA synthesis, reducing its activation. It can be suppressed by epigenetic modifications in the MYC promoter region. B) Targeting glycolysis 2-Deoxyglucose (2-DG) – Glucose analog that suppresses glycolysis. LDHA inhibitor – Blocks lactate formation, disrupting cancer cell metabolism. C) Inhibition of glutaminolysis CB-839 – Inhibits glutaminase, reducing the energy supply of MYC cells. D) Destabilization of MYC protein Amoqalib and PROTAC methods – Accelerates the degradation of MYC by the proteasome. 2.3. PI3K/AKT/mTOR pathway The PI3K/AKT/mTOR pathway is one of the main signaling pathways that control cell growth, survival, metabolism, and proliferation. This pathway plays an important role in cancer development, as its overactivation leads to uncontrolled

cell division, suppression of apoptotic processes, and metabolic reprogramming. 1. Main components of the PI3K/AKT/mTOR pathway This pathway consists of three main components: PI3K (phosphatidylinositol-3-kinase) AKT (Protein Kinase B) mTOR (Mammalian Target of Rapamycin) They work together and control signal transduction within the cell. 2. Activation and function of PI3K What is PI3K (Phosphatidylinositol-3-kinase)? PI3K is an enzyme that is activated by receptors on the cell surface, initiating a signaling pathway in the membrane. It is mainly activated by receptor tyrosine kinases (RTKs) and G-protein-coupled receptors (GPCRs). How is PI3K activated? 1. Pancreatic growth factor (IGF-1), epidermal growth factor (EGF), or other signals activate receptors on the cell surface. 2. These receptors activate PI3K. 3. PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). 4. PIP3, in turn, stimulates the translocation of AKT to the cell membrane. PI3K activation promotes cell survival and suppresses apoptosis. 3. Activation and metabolic effects of AKT What is AKT and how does it work? AKT is a serine/threonine kinase that affects cell survival, growth, and metabolic changes. Once activated, AKT: Inhibits GSK3β – this protein helps increase the metabolic activity of the cell. Inhibits BAD (a pro-apoptotic protein) – helps cells avoid death. Activates the mTOR pathway – this process increases protein synthesis and cell growth. Translocates GLUT4 to the membrane – which increases glucose transport and glycolysis. Overactivation of AKT allows cancer cells to grow rapidly by altering their metabolism. 4. Activation of mTOR and its effect on the growth process What is mTOR (Mammalian Target of Rapamycin)? mTOR is a serine/threonine kinase activated by AKT that controls cell growth, proliferation, and metabolic processes. mTOR forms two main complexes: mTORC1 – regulates protein synthesis and cell metabolism. mTORC2 – promotes full activation of AKT. Main functions of mTOR Increases protein synthesis – enhances ribosomal activity via S6K1 and 4E-BP1. Increases glucose metabolism – activates glycolysis enzymes via HIF-1α. Stimulates lipid biosynthesis – regulates fatty acid synthesis via SREBP1. Suppresses autophagy – which reduces the process of self-destruction of the cell. Constant activity of mTOR causes the growth of cancer cells. 5. The Relationship of the PI3K/AKT/mTOR Pathway to Cancer In cancer cells, the PI3K/AKT/mTOR pathway is often mutated or overactivated, which: Causes uncontrolled cell growth Suppresses apoptosis (programmed death) processes. Alters glucose and lipid metabolism. The PI3K/AKT/mTOR pathway has been found to be overactivated in the following types of cancer: Breast cancer Prostate cancer; Lung cancer; Liver cancer; Glioblastoma (brain cancer) 6. Targeting the PI3K/AKT/mTOR Pathway: Therapeutic Approaches Since overactivation of the PI3K/AKT/mTOR pathway accelerates the growth of cancer cells, many therapeutic strategies are aimed at inhibiting this pathway. A) PI3K

Inhibitors Alpelisib (BYL719) – Approved for breast cancer with PIK3CA mutations. Idelalisib – Used in malignant lymphomas. B) AKT Inhibitors Ipatasertib – Being tested in the treatment of prostate cancer. MK-2206 – Potential drug for breast cancer. C) mTOR Inhibitors Rapamycin (Sirolimus) – Inhibits mTORC1. Everolimus – Used in lung and kidney cancer. Temsirolimus – Approved for kidney cancer.7. The relationship between the PI3K/AKT/mTOR pathway and the Warburg effect The PI3K/AKT/mTOR pathway supports the Warburg effect: It activates glycolysis enzymes through HIF-1α. It increases the expression of GLUT1, accelerating glucose transport. It increases the expression of lactate dehydrogenase (LDHA), increasing lactate formation. This ensures that cancer cells can grow even under conditions of oxygen deprivation. 3. The Warburg effect and metabolic plasticity Mitochondrial metabolism is the main energy production process of the body and is an important part of the vital activity of cells. Especially in cancer therapy, it is one of the important strategies to weaken the Warburg effect and switch cancer cells from less efficient glycolysis to mitochondrial respiration by activating mitochondrial metabolism.



1.Main pathways of mitochondrial metabolism Mitochondrial metabolism includes the following main pathways: TCA (Krebs) cycle – The main energy-producing cycle of mitochondria, which produces ATP from acetyl-CoA. In cancer cells, this process may be

reduced compared to glycolysis. Oxidative phosphorylation (OXPHOS) – ATP is synthesized from ADP via the electron transport chain (ETC). The activity of complexes I - IV may be reduced in cancer cells. Beta-oxidation (catabolism of fatty acids) – Large amounts of ATP are produced as a result of the oxidation of fatty acids in mitochondria. Some cancer cells may switch to fat metabolism instead of glycolysis. Glutaminolysis – The amino acid glutamine can be used by cancer cells as a mitochondrial energy source. This process may be vital for cancer cells. 2. Methods to activate mitochondrial metabolism Stopping the Warburg effect The Warburg effect is when cancer cells rely on glycolysis instead of mitochondrial respiration. If cells switch back to mitochondrial metabolism, their energy production efficiency increases, which limits cancer cell growth by making them more dependent on oxygen. Agents used for this include: Dichloroacetate (DCA) – Inhibits pyruvate dehydrogenase kinase (PDK), directing pyruvate to the mitochondria. Metformin – Stimulates mitochondrial metabolism not only in diabetes but also in cancer, and reduces glucose dependence by affecting complex I. Oxidative phosphorylation activators (CoQ10, α-lipoic acid, NAD+, Riboflavin) – Stimulate mitochondrial function. Stimulate the electron transport chain (ETC) in mitochondria The electron transport chain (ETC) is essential for ATP production in mitochondria. Increasing its activity contributes to the efficient production of energy and an increase in the level of cell vitality. ETC activators: CoQ10 (Coenzyme Q10) – Stimulates the activity of Complex I and III. Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN) – Improves mitochondrial metabolism by increasing NAD+ levels. Mitochondrial antioxidants (MitoQ, SkQ1) – Protect mitochondria from oxidative stress and increase the efficiency of energy production. Stimulation of beta-oxidation Cells have the opportunity to obtain additional energy through the oxidation of fatty acids. Carnitine and Carnitine Palmitoyltransferase-1 (CPT-1) stimulators – Improve the entry of fatty acids into mitochondria. PPR-delta agonists (GW501516) – Enhance the breakdown of fatty acids. BCAA (leucine, isoleucine) – Amino acids improve mitochondrial metabolism. Increasing mitochondrial biogenesis Mitochondrial biogenesis is the process of creating new mitochondria, increasing the energy production capacity of cells. PGC-1α activators (Resveratrol, AICAR, NAD+) – Stimulate mitochondrial biogenesis, reducing the metabolic adaptation of cancer cells. Physical activity and aerobic exercise – Naturally increase PGC-1α and increase mitochondrial volume. SIRT1/NAD+ pathway – Sirtuins increase mitochondrial activity and stimulate cellular rejuvenation processes. 3. Clinical significance of activating mitochondrial metabolism In the context of cancer, activating mitochondrial metabolism can reduce the dependence of cells on glucose and change their energy sources. This helps to exploit the weaknesses of the Warburg effect and suppress the growth of cancer cells. Improving mitochondrial metabolism in

neurological diseases can support neuronal function by increasing the energy production capacity of cells in diseases such as Alzheimer's and Parkinson's. In cardiovascular health, increasing mitochondrial activity helps the heart muscle function efficiently and helps prevent heart disease. Stimulating mitochondrial metabolism for longevity and overall health improves the energy production processes of cells, reduces oxidative stress, and slows the aging process. 4. Therapeutic strategies targeting the Warburg effect Various metabolic therapy strategies have been developed to suppress cancer metabolism and induce cells to undergo apoptosis: 4.1. Glycolysis inhibitors Glycolysis inhibitors are substances or factors that slow down or stop the process of glycolysis, i.e. the conversion of glucose to pyruvate to produce energy. Glycolysis is an important metabolic pathway that occurs within the cell, in the cytoplasm, in which glucose is broken down to form energy molecules such as ATP (adenosine triphosphate) and NADH. Inhibitors affect cellular energetics by controlling or stopping this process. Glycolysis inhibitors work in several ways. They usually block specific enzymes in glycolysis or change the conditions necessary for the process. Here are a few key examples and their mechanisms of action: Enzyme inhibition: Each step in glycolysis is carried out by specific enzymes. For example, phosphofructokinase (PFK) is one of the main regulatory enzymes of glycolysis. If this enzyme is blocked by an inhibitor, the conversion of glucose to fructose-1,6-bisphosphate stops, which slows down the entire process. An example of such inhibitors is the high accumulation of ATP, because when the cell is rich in energy, the activity of PFC decreases to slow down glycolysis. Chemicals: Some chemical compounds can stop glycolysis. For example, 2-deoxyglucose is similar to glucose, but it is phosphorylated inside the cell and cannot proceed to the next steps. This substance causes glycolysis to stall at the beginning. Another example is iodoacetate, which blocks the enzyme glyceraldehyde-3-phosphate dehydrogenase and stops the energy-producing step of glycolysis. pH and acidity: Glycolytic enzymes work at a specific pH. If the environment inside the cell becomes too acidic or alkaline, the activity of the enzymes decreases, which inhibits glycolysis. For example, excessive accumulation of lactate can increase acidity and slow down the process. Oxygen effect: Although glycolysis is itself an anaerobic process, the presence of oxygen can indirectly affect it. Under oxygenated conditions, pyruvate is diverted to the mitochondria for oxidation, and the rate of glycolysis can decrease (the so-called Pasteur effect). Glycolysis inhibitors can occur naturally within the cell (e.g., as metabolites such as ATP or citrate) or as exogenous substances (chemical inhibitors). Their main purpose is to balance energy production or to control glycolysis in pathological conditions (e.g., in cancer cells). Cancer cells often rely more heavily on glycolysis (the Warburg effect), so inhibitors are important for research and treatment in this area.!4.2. Activation of mitochondrial

metabolism As a counter-strategy to the Warburg effect, drugs that activate mitochondrial metabolism are used: Metformin - inhibits the activity of mitochondrial complex I, disrupting the energy production of cancer cells Oxidative phosphorylation stimulants - direct cells to apoptosis 4.3. Combination therapy and personalized approaches The importance of combination therapy and personalized approaches in cancer treatment Cancer is a complex and multifactorial disease, in the treatment of which combination therapy (use of several methods) and a personalized approach (adaptation to the individual characteristics of the patient) play a key role. 1. Combination Therapy and Cancer Combination therapy increases the effectiveness of cancer treatment by attacking it from different directions at the same time. Methods Used: Chemotherapy + Radiation Therapy. Some tumors are sensitive to radiation, while others respond well to chemotherapy. Using them in combination gives better results. Immunotherapy + Targeted Therapy - Immunotherapy (e.g., PD-1/PD-L1 inhibitors) activates the immune system, while targeted therapy (e.g., EGFR inhibitors) stops the growth of tumor cells. Chemotherapy + Hormone Therapy (for breast cancer) - Hormone therapy is used in combination with chemotherapy in patients with hormone receptors (+). CAR-T cell therapy + Cytokine therapy - In some leukemias and lymphomas, genetically modified T-cells (CAR-T) are used in combination with anti-inflammatory drugs. Advantages: Reduces drug resistance (tumor cells cannot withstand multiple attacks at once). Accelerates tumor regression and is good at preventing metastases. 2. Personalized Approach and Cancer Since each cancer patient's genetic makeup and tumor biology are different, standard treatments are not always effective. A personalized approach includes: a) Genetic Tests and Biomarkers Tumor DNA sequencing (Next-Generation Sequencing, NGS) – to identify mutations in the tumor (e.g. BRCA, EGFR, KRAS). PD-L1 testing – to predict response to immunotherapy. Microsatellite instability (MSI testing) – to indicate the effectiveness of immunotherapy in some types of cancer. b) Individual Treatment Plans Targeted therapy – if the tumor has a specific mutation (e.g. Crizotinib for ALK+ lung cancer). Immunotherapy – for patients with high PD-L1 (Pembrolizumab, Nivolumab). Hormone therapy – if breast or prostate cancer has hormone receptors (+). c) Minimally Invasive Diagnostics (Liquid Biopsy). "Liquid biopsy" – detection of tumor DNA through blood, which helps to detect metastases early. 3. Future Prospects - With the help of AI (Artificial Intelligence), cancer prognosis and treatment plans are being predicted more accurately. - CRISPR genetic editing – new methods are being developed to destroy tumor cells. - Personalized vaccines – individual cancer vaccines are being tested for each patient. 5. Future prospects and scientific challenges. The importance of the Warburg effect in oncological practice is increasing. At the same time, there are several problems in therapeutic targeting of cancer metabolism: Glycolysis is a universal metabolic pathway – it

is difficult to target only cancer cells without damaging healthy cells; Metabolic plasticity and resistance – cancer cells have the ability to adapt to metabolic therapy; The need for personalized therapy – each patient’s cancer metabolism may be unique; future research should focus on understanding the role of the Warburg effect in individual cancers, developing personalized metabolic therapies, and developing new drugs that balance glycolysis and oxidative metabolism.

Conclusion

Cancer cells are distinct from normal cells and maintain their growth and viability by altering their metabolic processes. The Warburg effect plays a central role in this process, as cancer cells rely on aerobic glycolysis for energy even when oxygen is available. This phenomenon is associated with factors such as oncogene activation, tumor suppressor gene inactivation, mitochondrial dysfunction, and hypoxia. A deeper understanding of the Warburg effect opens up new possibilities for cancer diagnosis and therapy. Metabolic plasticity of cancer cells can be disrupted by glycolysis inhibitors (e.g., 2-deoxyglucose) and metabolic therapy (e.g., dichloroacetate). At the same time, by stimulating mitochondrial metabolism, cells can be directed towards apoptosis. In the future, further study of the Warburg effect will help to formulate new approaches in oncology. In particular, evaluating the effectiveness of personalized metabolic therapy and combination treatment strategies remains one of the current areas of interest. New drugs and genetic manipulations targeting cancer metabolism may lead to the development of personalized therapies. Future developments in cancer research will lead to a deeper understanding of the impact of metabolic alterations on diagnosis, therapy, and prognosis. Therefore, a detailed study of the Warburg effect and the development of strategies to effectively target it will remain an important scientific priority for the future development of oncology.

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