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BIOCHEMICAL PATHWAYS IN CANCER METABOLISM: IMPLICATIONS FOR THERAPEUTIC TARGETING

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ABSTRACT
Our distinct metabolic reprogramming of cancer cells supports their rapid growth and survival. In this review, we focus on the metabolic pathway alterations that include glycolysis, tricarboxylic acid (TCA) cycle, lipid metabolism, and amino acid metabolism which define tumor development. With advances in metabolic imaging and biomarkers, we know better what goes wrong and are able to detect and monitor cancer earlier. Discussion of current and emerging therapeutic approaches to target metabolic vulnerabilities, including inhibitors of glycolysis, glutaminolysis, fatty acid synthesis and IDH mutations, is included. Redox modulation and immunometabolism also present promising avenues for personalized cancer therapy, these strategies along with the others. Our strategy takes advantage of the inherent metabolic differences between normal and tumor cells to develop more effective interventions than before, aimed at improving patient outcomes.

INTRODUCTION

In recent years, cancer metabolism has become an area of intense interest as it is key to supporting the rapid cell growth and survival found in the tumor microenvironment. Unlike normal cells, cancer cells reprogram their metabolism extensively to meet their greatly increased energy and biosynthetic demands. The process of this reprogramming is characterized by changes in multiple biochemical pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, lipid metabolism and amino acid metabolism.[1-3]

The Warburg effect is one of the most characteristic features of cancer metabolism — one in which cancer cells ferment for energy production when the presence of much oxygen is present. This metabolic shift advocates for the anabolic growth necessary for rapid tumor proliferation. In addition, cancer cells tend to also have altered glutamine metabolism, impaired lipid biosynthesis, and changed mitochondria, attributes that give these cells an advantage while living in the harsh environment.[4,5]

To identify potential therapeutic targets one must understand these metabolic alterations. The idea is to develop treatments that target certain enzymes or pathways that are out of whack in cancer cells — and, unlike chemotherapy, would selectively interfere with the metabolism of the cancer cells without disrupting normal cells. Thus, this review will take in the main biochemical pathway involved in cancer metabolism and what implications they have for therapeutic targeting.

GLYCOLYSIS AND THE WARBURG EFFECT

Historical Background

Originally described by Otto Warburg in the 1920s, The Warburg Effect explains that cancer cells take in more glucose and mainly convert it to lactate, even when oxygen is present. In contrast to normal cells, whose energy production largely depends on oxidative phosphorylation when oxygen is available, this metabolic shift is against normal cell behavior.[5-7]

Mechanisms and Regulation

Several key mechanisms and regulatory factors contribute to the Warburg Effect:[6, 8-10]

- Activation of Oncogenes: The MYC and KRAS oncogenes boost the expression of glycolytic enzymes and enhance glucose metabolism.
- Loss of Tumor Suppressors: Cancer cells commonly have mutations or inactive forms of tumor suppressors such as TP53 that normally reduce glycolysis.
- Hypoxia-Inducible Factors (HIFs): Hypoxic stabilization and activation of HIF transcription of glycolysis and glucose transport genes.

Key Enzymes and Transporters[11-16]

- Hexokinase 2 (HK2): Catalyzes the first step of glycolysis, converting glucose to glucose-6-phosphate.
- Phosphofructokinase-1 (PFK1): A rate-limiting enzyme that regulates the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate.
- Pyruvate Kinase M2 (PKM2): Facilitates the final step of glycolysis, producing pyruvate and ATP.
- Glucose Transporters (GLUTs): GLUT1 and GLUT3 are often overexpressed in cancer cells, increasing glucose uptake.

Impact on Tumor Growth[5,17-20]

The Warburg Effect supports tumor growth through several mechanisms:

- Rapid ATP Production: Glycolysis may, admittedly, be less efficient than oxidative phosphorylation, but it does provide a rapid clearance of ATP to support rapid cell division.
- Biosynthetic Precursors: The pathways to generate nucleotides, amino acids and lipids needed for cell proliferation utilize glycolytic intermediates that are redirected away from normal glucose metabolism.
- Lactate Production: Its lactate acidifies the tumor microenvironment to promote invasion and metastasis and limit the function of immune cells.

Therapeutic Implications[21-24]

Targeting glycolysis and the Warburg Effect offers several therapeutic strategies:

- Inhibition of Glycolytic Enzymes: reduce glycolytic flux with compounds such as 2-deoxy-D-glucose (2-DG) that inhibit hexokinase.
- Blocking Lactate Production: The inhibitors of lactate dehydrogenase (LDH) act to reduce lactate accumulation and its associated pro tumor effects.
- Exploiting Metabolic Dependencies: Therapies that interfere with glycolysis are especially effective against cells that are relying on glycolysis for. For instance, dichloroacetate (DCA) activates pyruvate dehydrogenase thus shifting metabolism towards oxidative phosphorylation.

TCA Cycle Alterations in Cancer

Overview

Tricarboxylic Acid (TCA) cycle also known as Krebs cycle or citric acid cycle is a central metabolic pathway involved in the energy production, biosynthesis and cellular respiration. Metabolic reprogramming in cancer cells includes categories of alterations in the TCA cycle that aid in the rapid proliferation and survival under adverse conditions.[25,26]

Key Enzymatic Alterations

Isocitrate Dehydrogenase (IDH) Mutations: Common mutations of IDH1 IDH2 in some cancers result in production of the oncometabolite 2-hydroxyglutarate (2-HG). Besides the CRBN itself, another metabolite of the CRBN can inhibit DNA and histone demethylation, thereby promoting tumorigenesis.[27,28]

Fumarate Hydratase (FH) Deficiency: The loss of FH activity results in accumulation of fumarate, a putative oncometabolite, that leads to the stabilization of HIF1α and subsequent enhancement of glycolysis and angiogenesis.[29]

Succinate Dehydrogenase (SDH) Mutations: Mutations in SDH cause the accumulation of succinate, another oncometabolite that inhibits prolyl hydroxylase enzymes, stabilizing HIF-1α and promoting a glycolytic phenotype.[30]

Impact on Tumor Growth[31-33]

Energy Production: Cancer cells however, whilst relying predominantly on glycolysis for the rapid production of ATP, require the TCA cycle as an ongoing source of metabolic intermediates for biosynthesis.

Biosynthetic Precursor Supply: Lipid synthesis utilizes TCA cycle intermediates such as citrate, amino acid and nucleotide biosynthesis utilize TCA cycle intermediates and the TCA cycle intermediates are refocused from normal anabolic pathways for intermediary metabolism..

Redox Balance: Oxidative phosphorylation is dependent on providing reducing equivalents (NADH and FADH2), obtained from the TCA cycle, to detoxify reactive oxygen species (ROS).

Therapeutic Implications[1,31,34-37]

Targeting TCA cycle alterations in cancer offers several therapeutic strategies:

IDH Inhibitors: According to the author, drugs such as ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) decrease 2-HG levels and restore normal cellular differentiation, targeting mutant IDH enzymes.

FH and SDH Restoration: Restoration or compensation of the function loss of FH and SDH might mitigate the effects of their respective oncometabolites through strategies.

Metabolic Pathway Modulators: Inhibition of metabolic flexibility of cancer cells can be achieved by modulating agents that alter the TCA cycle and interactions between the TCA cycle and other metabolic pathways.

Table 1: TCA Cycle Alterations in Cancer.

Section	Details
Overview	The TCA cycle, also known as the Krebs cycle or citric acid cycle, is crucial for energy production, biosynthesis, and cellular respiration. In cancer, alterations in the TCA cycle aid in rapid proliferation and survival.
Key Enzymatic Alterations	
IDH Mutations	Mutations in IDH1 and IDH2 result in the production of 2-hydroxyglutarate (2-HG), which inhibits DNA and histone demethylation and promotes tumorigenesis.
FH Deficiency	Loss of FH activity causes fumarate accumulation, acting as an oncometabolite that stabilizes HIF-1α, enhancing glycolysis and angiogenesis.
SDH Mutations	Mutations in SDH result in succinate accumulation, inhibiting prolyl hydroxylase enzymes, stabilizing HIF-1α, and promoting a glycolytic phenotype.
Impact on Tumor Growth	
Energy Production	Cancer cells rely on glycolysis for rapid ATP production, but the TCA cycle remains essential for generating metabolic intermediates needed for biosynthesis.
Biosynthetic Precursor Supply	TCA cycle intermediates like citrate are used for lipid synthesis; other intermediates aid in amino acid and nucleotide biosynthesis.
Redox Balance	The TCA cycle provides reducing equivalents (NADH and FADH2) crucial for oxidative phosphorylation, helping detoxify reactive oxygen species (ROS).
Therapeutic Implications	
IDH Inhibitors	Drugs like ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) target mutant IDH enzymes, reducing 2-HG levels and restoring normal cellular differentiation.
FH and SDH Restoration	Strategies to restore or compensate for the loss of FH and SDH function could mitigate the effects of their respective oncometabolites.
Metabolic Pathway Modulators	Agents that alter the TCA cycle and its interactions with other metabolic pathways can disrupt the metabolic flexibility of cancer cells.

Lipid Metabolism in Cancer

Overview

Lipid metabolism is crucial for maintaining cellular membrane integrity, energy storage, and signal transduction. In cancer cells, lipid metabolism is reprogrammed to support rapid proliferation, survival, and metastasis. These alterations include increased lipid synthesis, uptake, and storage, as well as enhanced fatty acid oxidation.[38-42]

Key Alterations in Lipid Metabolism[43-47]

Fatty Acid Synthesis: According to Oncotarget, cancer cells often have elevated activity of enzymes that lead to de novo fatty acid synthesis, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC).

Lipid Uptake: Increase uptake of exogenous lipids is facilitated by exogenous lipid overexpression of lipid transporters like CD36 and low-density lipoprotein receptor (LDLR).

Lipid Storage: The ability of cancer cells to store excess lipids in lipid droplets, allowing them to re-mobilize the lipids under metabolic stress, is further promoted.

Fatty Acid Oxidation (FAO): Thus, upregulation of enzymes of FAO, such as carnitine palmitoyltransferase 1 (CPT1) can supply alternative energy for cancer cells.

Impact on Tumor Growth[48-52]

Membrane Biosynthesis: Cellular membranes are essential for lipids. Lipid synthesis is enhanced to maintain an adequate membrane lipid supply for the rapid proliferation of cancer cells.

Energy Production: ATP and NADPH are critical for maintaining cellular energy requirements for rapidly proliferating tumor cells, and are provided by FAO.

Signaling Pathways: In cell signaling pathways that are important for growth, survival or metastasis, lipid derived signaling molecules including phosphatidylinositol (PI) and sphingolipids have important functions.

Tumor Microenvironment: Modulation of immune cell function as well as inflammation can be achieved by altered lipid metabolism, which can then influence the tumor microenvironment.

Therapeutic Implications[38,44,45,53-55]

Targeting lipid metabolism in cancer provides several promising therapeutic strategies:

Inhibition of Fatty Acid Synthesis: Drugs including orlistat (a FASN inhibitor) and ACC inhibitors are trying to block de novo fatty acid synthesis.

Blocking Lipid Uptake: By blocking uptake of exogenous lipids using specific inhibitors of lipid

transporters, such as CD36, uptake of exogenous lipids can be targeted.
Disrupting FAO: Falling back on alternative means of energy, CAIs, like etomoxir, can disuse FAO and thus reduce the amount of energy available to cancer cells.
Modulating Lipid Signaling: Disrupting the oncogenic signaling driven by lipid-derived molecules with drugs that target lipid signaling pathways.

Table 2: Lipid Metabolism in Cancer.

Section	Details
Overview	Cellular membrane integrity, energy storage, and signal transduction all rely upon function of lipid metabolism. Lipid metabolism is reprogrammed in cancer cells to facilitate rapid proliferation and survival as well as metastasis.
Key Alterations in Lipid Metabolism	
Fatty Acid Synthesis	Enzymes which are for cancer cells often have high activities, for example, fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC).
Lipid Uptake	It facilitates increased uptake of exogenous lipids, which can occur overexpression of lipid transporters, such as CD36 and low density lipoprotein receptor (LDLR).
Lipid Storage	Enhanced formation of lipid droplets allows cancer cells to store excess lipids, which can be mobilized during metabolic stress.
Fatty Acid Oxidation (FAO)	Upregulation of enzymes involved in FAO, such as carnitine palmitoyltransferase 1 (CPT1), provides an alternative energy source for cancer cells.
Impact on Tumor Growth	
Membrane Biosynthesis	Lipids are essential components of cellular membranes. Increased lipid synthesis supports the rapid proliferation of cancer cells by ensuring an adequate supply of membrane lipids.
Energy Production	FAO provides ATP and NADPH, which are critical for sustaining the energy needs of rapidly proliferating tumor cells.
Signaling Pathways	Lipid-derived signaling molecules, such as phosphatidylinositol (PI) and sphingolipids, play key roles in cell signaling pathways that regulate growth, survival, and metastasis.
Tumor Microenvironment	Altered lipid metabolism can influence the tumor microenvironment by modulating immune cell function and promoting inflammation.
Therapeutic Implications	
Inhibition of Fatty Acid Synthesis	Drugs like orlistat (a FASN inhibitor) and ACC inhibitors aim to block de novo fatty acid synthesis.
Blocking Lipid Uptake	Targeting lipid transporters such as CD36 with specific inhibitors can reduce the uptake of exogenous lipids.
Disrupting FAO	Inhibitors of CPT1, like etomoxir, can impair FAO and reduce the energy supply to cancer cells.
Modulating Lipid Signaling	Drugs that target lipid signaling pathways can disrupt the oncogenic signaling driven by lipid-derived molecules.

Amino Acid Metabolism in Cancer

Overview

Amino acid metabolism is essential for cell growth, maintenance, and repair. Cancer cells reprogram amino acid metabolism to meet their heightened demands for rapid proliferation and survival. These alterations include increased uptake, synthesis, and catabolism of specific amino acids.[5,31,56-59]

Table 3: Amino Acid Metabolism in Cancer.

Section	Details
Overview	Amino acid metabolism is essential for cell growth, maintenance, and repair. Cancer cells reprogram amino acid metabolism to meet their heightened demands for rapid proliferation and survival.
Key Alterations in Amino Acid Metabolism	
Glutamine Addiction	Many cancer cells exhibit a high dependency on glutamine, serving as a carbon and nitrogen source for biosynthesis and anaplerosis.
Serine and Glycine	Cancer cells often upregulate the synthesis and utilization of serine and

Metabolism	glycine, contributing to nucleotide and protein synthesis as well as one-carbon metabolism.
BCAAs	Increased catabolism of branched-chain amino acids (leucine, isoleucine, and valine) provides intermediates for the TCA cycle and supports energy production.
Arginine and Proline Metabolism	Altered metabolism of these amino acids can affect nitric oxide production and collagen synthesis, impacting tumor microenvironment remodeling.
Impact on Tumor Growth	
Biosynthetic Precursors	Amino acids are essential building blocks for proteins, nucleotides, and other macromolecules required for cell proliferation.
Redox Balance	Amino acids like glutamine contribute to the production of reducing agents (e.g., NADPH), helping maintain redox balance and protect against oxidative stress.
Signaling Pathways	Certain amino acids activate mTOR and other signaling pathways that regulate cell growth and survival.
Anaplerosis	The replenishment of TCA cycle intermediates via amino acid catabolism supports metabolic flexibility and energy production.
Therapeutic Implications	
Glutaminase Inhibitors	Drugs like CB-839 inhibit glutaminase, reducing glutamine conversion to glutamate and disrupting cancer cell metabolism.
Inhibition of Serine/Glycine Synthesis	Targeting enzymes like phosphoglycerate dehydrogenase (PHGDH) can reduce serine and glycine availability, affecting nucleotide synthesis.
BCAA Catabolism Inhibitors	Inhibiting enzymes involved in BCAA catabolism can reduce TCA cycle replenishment and energy production.
Arginine Deprivation	Agents like pegylated arginine deiminase (ADI-PEG 20) deplete arginine, exploiting the inability of certain cancer cells to synthesize arginine.

Advances in Metabolic Imaging and Biomarkers in Cancer

Overview

Early detection, diagnosis, and monitoring of cancer all require metabolic imaging and biomarkers. These technologies have continued to advance and now we better understand the tumor metabolism and additional avenues for personalized cancer therapy. As such these tools can be used to visualize metabolic processes in real time and also identify certain biomarkers involved in cancer metabolism.[60-62]

Table 4: Advances in Metabolic Imaging and Biomarkers in Cancer.

Section	Details
Overview	Metabolomics and biomarkers are needed to detect early, diagnose and monitor cancer. These technologies have advanced so that we understand more about tumor metabolism and have new ways to develop personalized cancer therapy.
Metabolic Imaging Techniques	
Positron Emission Tomography (PET)	
18F-FDG PET	18F-FDG PET for oncology is the most widely used metabolic imaging technique.
Other PET Tracers	Additional metabolic information is added with tracers such as 18F-FLT (thymidine uptake) and 18F-FMISO (hypoxia).
Magnetic Resonance Spectroscopy (MRS)	A non-invasive technique to measure the concentrations of metabolites such as lactate, choline and creatine in tissue.
Hyperpolarized MRI	It enhances the signal of certain metabolites to enable real time observation of metabolic processes, such as pyruvate to lactate conversion.
Optical Imaging	Applications of fluorescence and bioluminescence imaging techniques to noninvasively couple metabolic changes and enzyme activities in live cells or animal models.

Metabolic Biomarkers	
Circulating Tumor Cells (CTCs) and DNA (ctDNA)	Detection of CTCs and ctDNA can provide insights into tumor metabolism and genetic alterations.
Metabolites in Blood and Urine	Specific metabolites, such as lactate, glutamine, and oncometabolites like 2-hydroxyglutarate (2-HG), serve as biomarkers for cancer diagnosis and prognosis.
Enzyme Levels	Elevated levels of enzymes like hexokinase, lactate dehydrogenase (LDH), and isocitrate dehydrogenase (IDH) indicate altered metabolic states in cancer cells.
Lipid Profiles	Altered lipid metabolism monitored through changes in lipid profiles in blood provides potential biomarkers for cancer.
Implications for Cancer Management	
Early Detection	Advanced metabolic imaging techniques can detect tumors at early stages by identifying areas of altered metabolism.
Treatment Monitoring	Metabolic changes resulting are monitored to evaluate efficacy of treatment and therapeutic strategies.
Personalized Therapy	Development of targeted therapies based on individual metabolic profile is enabled by the identification of the specific metabolic biomarkers.
Prognosis	Prognostic biomarkers from metabolism help detect impending disease and patient outcomes.

Current and Emerging Therapeutic Approaches in Cancer Metabolism

Overview

In the setting of distinct metabolic alterations in tumor cells, targeting cancer metabolism has become a promising therapeutic strategy. These metabolic vulnerabilities are being exploited to selectively inhibit cancer cell growth and survival by current and emerging therapies.

Table 5: Current and Emerging Therapeutic Approaches in Cancer Metabolism.

Section	Details
Overview	Metabolic alterations in tumor cells have made targeting cancer metabolism an emerging and promising therapeutic strategy. Attempts are underway to capitalize on these metabolic vulnerabilities to develop current and emergent therapies that either poison the cancer cell by specifically killing it, or force it into apoptosis without harming normal cells.
Current Therapeutic Approaches	
Glycolysis Inhibitors	
2-Deoxy-D-Glucose (2-DG)	An analog of glucose that inhibits hexokinase, the first enzyme in glycolysis, thereby reducing glycolytic flux.
Lonidamine	Targets hexokinase and mitochondrial function, disrupting energy production in cancer cells.
TKI258	Inhibits glycolytic enzymes and reduces lactate production.
Glutaminase Inhibitors	
CB-839 (Telaglenastat)	Inhibits glutaminase, reducing the conversion of glutamine to glutamate and disrupting glutamine metabolism.
Fatty Acid Synthesis Inhibitors	
Orlistat	Inhibits fatty acid synthase (FASN), reducing lipid synthesis required for membrane formation and signaling.
TVB-2640	A FASN inhibitor currently under clinical investigation for various cancers.
IDH Inhibitors	
Ivosidenib (AG-120)	Targets mutant IDH1, reducing the production of the oncometabolite 2-hydroxyglutarate (2-HG).
Enasidenib (AG-221)	Inhibits mutant IDH2, lowering 2-HG levels and promoting cellular differentiation.
Arginine Deprivation	
ADI-PEG 20	Pegylated arginine deiminase that depletes arginine, exploiting the inability

	of certain cancers to synthesize this amino acid.
Emerging Therapeutic Approaches	
Redox Modulation	
APR-246 (Eprenetapopt)	Restores p53 function and induces ROS production, leading to cancer cell death.
ATN-224	A copper chelator that disrupts superoxide dismutase 1 (SOD1) activity, increasing oxidative stress in cancer cells.
Mitochondrial Targeting	
Metformin	Commonly used for diabetes, it targets mitochondrial complex I, reducing oxidative phosphorylation and ATP production in cancer cells.
BAY 87-2243	Inhibits mitochondrial complex I, leading to decreased ATP production and increased ROS.
Autophagy Inhibition	
Hydroxychloroquine (HCQ)	Inhibits autophagy, a process that cancer cells use to recycle nutrients under metabolic stress.
Lys05	A more potent autophagy inhibitor currently under preclinical investigation.
Immunometabolism	
IDO Inhibitors	Target indoleamine 2,3-dioxygenase (IDO), an enzyme that modulates tryptophan metabolism and immune evasion.
Arginase Inhibitors	Block arginase activity, enhancing immune response by increasing arginine availability for T-cell activation.
Combination Therapies	
Combination with Chemotherapy or Targeted Therapies	Combining metabolic inhibitors with traditional chemotherapy or targeted therapies to enhance efficacy and overcome resistance.
Combination with Immune Checkpoint Inhibitors	Combining metabolic inhibitors with immune checkpoint inhibitors to enhance anti-tumor immunity.

CONCLUSION

Metabolic alterations in cancer cells represent promising therapeutic strategies for interference with tumor growth and improvement of treatment efficacy. Since they understand cancer metabolism so much better, there are now many different inhibitors for glycolysis, glutaminase, fatty acid synthesis and even inhibitors for IDH mutations. Tighter options for treating PKC are offered by emerging approaches such as redox modulation and immunometabolism. These strategies take advantage of the specific metabolic vulnerability of cancer to improve patient outcomes and tailor therapy in this ongoing war against cancer.

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