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Review Article

Elucidating the Nexus of Mitochondrial Dysfunction and Oncometabolite Accumulation in Tumorigenesis.

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Abstract

Cancer is a complex disease driven by disruptions in cellular metabolism and mitochondrial function, enabling malignant cells to proliferate unchecked, evade apoptosis, and metastasize to distant organs. This exhaustive review elucidates the metabolic dysregulations inherent to cancer, with a particular focus on mitochondrial dysfunction, the accumulation of oncometabolites, and the reprogramming of metabolic pathways. A comprehensive literature search was conducted across major scientific databases, including PubMed, Web of Science, Scopus, and ScienceDirect, spanning January 2010 to March 2025. Controlled vocabulary and Boolean operators were employed to capture relevant studies, focusing on cancer metabolism, metabolic reprogramming, tumour markers, oncometabolites, mitochondrial dysfunction, and regulatory pathways. Extracted data were organized into thematic areas, and a qualitative synthesis approach was used to integrate findings, identifying common mechanistic patterns underlying tumour initiation, progression, and metastasis. The Warburg effect, a typical feature of cancer metabolism, is characterized by a predilection for aerobic glycolysis, thereby supporting biosynthetic processes and contributing to tumour microenvironment acidification and immune suppression. Mitochondrial dysfunction triggers genomic instability and oncogenic transformation. Meanwhile, oncometabolites like 2-hydroxyglutarate, fumarate, and sarcosine disrupt cellular signalling and epigenetic regulation, promoting tumour growth and progression. The clinical significance of tumour markers and metabolic biomarkers is underscored, and the systemic metabolic sequelae of cancer, including cancer-associated cachexia, are expounded upon. In glioblastoma, Aurora kinase A inhibition reverses the Warburg effect, decreasing glucose uptake and boosting oxidative phosphorylation. Cancer-associated fibroblasts exhibit aerobic glycolysis, promoting tumor growth and metastasis via the reverse Warburg effect. Glycolysis inhibition suppresses tumor growth in pancreatic cancer, and the Warburg effect contributes to chemoresistance by upregulating glycolytic enzymes and increasing lactate production. Targeting the Warburg effect, including inhibiting glycolytic enzymes and modulating mitochondrial function, offers potential therapeutic strategies for cancer treatment. This review provides a comprehensive exposition of the biochemical mechanisms underpinning metabolic derangements in cancer, which may unveil novel avenues for diagnostic and therapeutic interventions.

Keywords: Cancer, Mitochondrial Dysfunction, Oncometabolites, Warburg Effect, Metabolic Reprogramming, Cachexia; Aurora kinase A, glioblastoma

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Introduction

Cancer remains a quintessential exemplar of a complex and devastating disease, afflicting humanity with an ever-increasing incidence and a staggering toll of morbidity and mortality. [1] The global burden of cancer is characterized by millions of new cases diagnosed annually, with concomitant mortality rates that underscore the pressing need for enhanced understanding and therapeutic innovation.[2] The biological intricacy of cancer stems from its capacity to evolve through a plethora of molecular alterations, thereby enabling malignant cells to proliferate uncontrollably, invade contiguous tissues, and metastasize to distant organs. [3] Notwithstanding significant advances in molecular biology, immunotherapy, and targeted therapeutics, metastatic cancers remain recalcitrant to treatment, with improved survival outcomes often predicated on early detection rather than curative interventions for advanced disease.[4]

Historically, the genetic paradigm has dominated cancer research, positing that the disease arises from the accumulation of mutations affecting key regulatory genes.[5] However, a burgeoning body of evidence from biochemical and metabolic studies has catalyzed a resurgence of interest in the metabolic theory of cancer, which posits that oncogenic processes are inextricably linked to disturbances in cellular energy metabolism.[6] This perspective underscores the profound metabolic reprogramming that occurs within tumour cells, highlighting the pivotal role of metabolic pathways in determining tumour growth, survival, and systemic disease manifestations.[7] The dysregulation of mitochondrial function, in particular, has emerged as a critical determinant of cancer pathogenesis, with oncometabolites and tumour markers serving as key effectors of disease progression.[8]

Furthermore, the interplay between genetic and metabolic alterations in cancer cells gives rise to a complex metabolic landscape that fosters tumour heterogeneity and therapeutic resistance. [9] The tumour microenvironment, comprising cancer-associated fibroblasts, immune cells, and endothelial cells, also plays a crucial role in shaping cancer metabolism and modulating treatment responses. [10] Elucidating the intricate relationships between mitochondrial dysfunction, oncometabolites, and tumour marker biology is essential for the development of novel diagnostic and therapeutic strategies that target the metabolic vulnerabilities of cancer cells. [11] Ultimately, a comprehensive understanding of cancer metabolism holds promise for improving treatment outcomes and reducing the global burden of this devastating disease

Materials and Methods

This review was conducted using a structured and systematic approach to ensure methodological rigor, transparency, and reproducibility. A comprehensive literature search was performed across major scientific databases, including PubMed, Web of Science, Scopus, and ScienceDirect, covering publications from January 2010 to March 2025. The search strategy employed controlled vocabulary, such as Medical Subject Headings, and well-defined Boolean operators to enhance sensitivity and specificity, incorporating key terms related to cancer metabolism, metabolic reprogramming, tumour markers, oncometabolites, mitochondrial dysfunction, and major regulatory pathways. Additional relevant studies were identified through manual screening of reference lists. Clear inclusion and exclusion criteria guided study selection, with only peer-reviewed original research articles, systematic reviews, and meta-analyses published in English providing biochemical, molecular, or clinical insights into cancer metabolism included. Conference abstracts without full texts, editorials, opinion articles, duplicates, and studies unrelated to metabolic aspects of cancer were excluded.

Retrieved records were exported, duplicates removed, and titles and abstracts screened based on predefined criteria, followed by full-text evaluation of potentially eligible studies. Final inclusion was determined through critical assessment, with discrepancies resolved through careful evaluation to minimize bias. Data extraction focused on key study characteristics, including metabolic pathways, molecular mechanisms, tumour markers, and clinical relevance, with extracted information organized into major thematic areas. A qualitative synthesis approach was employed, integrating findings through comparative biochemical

analysis to identify common mechanistic patterns underlying tumour initiation, progression, and metastasis. The study selection process adhered to PRISMA guidelines, with a PRISMA flow diagram incorporated to illustrate the identification, screening, eligibility, and inclusion stages. Although prospective registration in PROSPERO was not undertaken, the review adhered to a predefined methodological framework aligned with PRISMA recommendations.

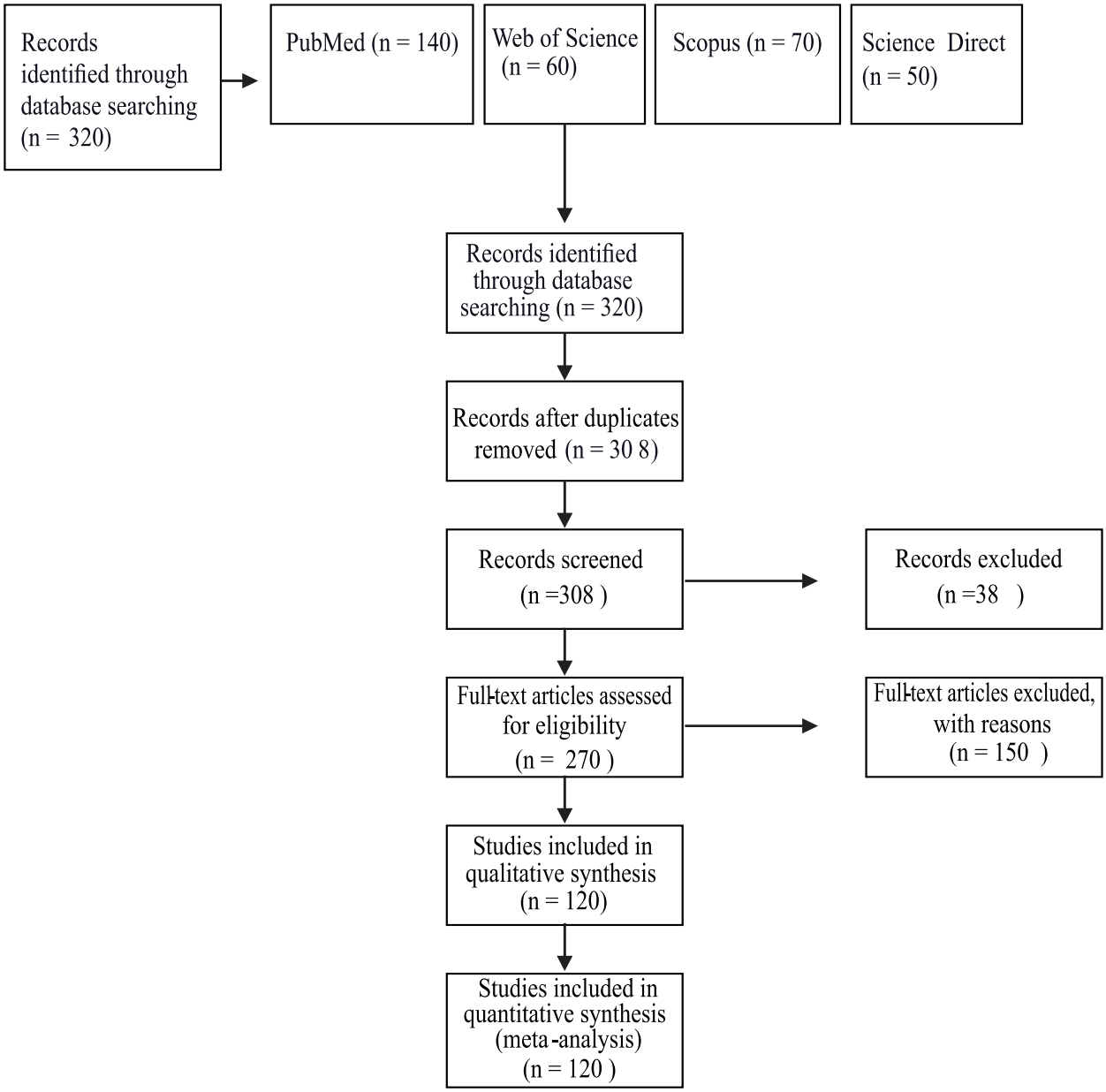

Figure 1: PRISMA Flow Diagram

Cancer as a Genetic Disease.

The genetic paradigm of cancer posits that carcinogenesis is a multistep process driven by the sequential acquisition of mutations in oncogenes and tumour suppressor genes, thereby disrupting the homeostatic regulation of cell proliferation, differentiation, and apoptosis.[12] Oncogenes, typically mutated or overexpressed forms of proto-oncogenes, promote cell growth and proliferation through diverse signalling pathways. [13]For instance, KRAS, a member of the RAS family, encodes a GTPase that participates in

signal transduction cascades, while BRAF, a serine/threonine kinase, is a key component of the mitogen-activated protein kinase (MAPK) pathway.[14] Additionally, MYC, a transcription factor, regulates a broad spectrum of genes involved in cell growth, metabolism, and ribosomal biogenesis, thereby exerting a profound influence on cellular metabolism and proliferation.[15]

Conversely, tumour suppressor genes, such as TP53, PTEN, and APC, function as negative regulators of cell proliferation, maintaining genomic stability and preventing uncontrolled cell growth. [16]TP53, often referred to as the "guardian of the genome," plays a pivotal role in DNA damage sensing, cell cycle arrest, and apoptosis, while PTEN regulates the phosphatidylinositol-3-kinase (PI3K) signalling pathway, a critical regulator of cell survival and metabolism.[17] APC, a component of the Wnt/β-catenin pathway, regulates β-catenin stability and modulates transcriptional programs involved in cell proliferation and differentiation. [18] Notwithstanding the explanatory power of the genetic model, large-scale genomic sequencing has unveiled extraordinary genetic heterogeneity across different cancers, with millions of mutations, thousands of gene fusions, and numerous chromosomal rearrangements identified across tumour genomes.[19]Landmark efforts, including The Cancer Genome Atlas and the International Cancer Genome Consortium, have revealed that tumours of similar histological origin exhibit vastly disparate mutational landscapes, often lacking a universal driver mutation.[20] This heterogeneity poses a fundamental limitation to the genetic theory, complicating the identification of consistent therapeutic targets and contributing to the transient clinical benefits of mutation-targeted therapies due to rapid resistance emergence.[21] For instance, BRAF V600E mutations in melanoma are effectively targeted by inhibitors such as vemurafenib, yet resistance frequently develops through metabolic rewiring and alternative pathway activation, underscoring the insufficiency of genetic targeting alone.[22] Similarly, KRAS mutations have long been refractory to therapeutic targeting, highlighting the limitations of a gene-centric approach. These findings suggest that genetic alterations may arise secondary to epigenetic modifications, environmental cues, or metabolic dysregulation, creating a permissive environment for tumourigenesis. [23] Indeed, metabolic stress and reactive oxygen species (ROS) generated from dysfunctional mitochondria can induce DNA damage and genomic instability, acting upstream of mutational events.[24] The tumour microenvironment, comprising cancer-associated fibroblasts, immune cells, and endothelial cells, plays a crucial role in shaping cancer evolution and modulating treatment responses. [25] Hypoxic tumour niches, for example, stabilize hypoxia-inducible factors, altering metabolism, promoting genetic instability, and driving angiogenesis. [26]This interplay between genetic and non-genetic factors underscores the complexity of tumourigenesis, highlighting the need for a more comprehensive understanding of cancer biology that incorporates insights from genomics, epigenomics, and metabolomics to develop effective therapeutic strategies.

Metabolic Theory of Cancer

The metabolic theory of cancer posits that malignant transformation is inextricably linked to perturbations in cellular energy metabolism and mitochondrial function, driving tumourigenesis. [27] Cancer cells undergo extensive metabolic reprogramming to sustain rapid proliferation and survival under stressful microenvironmental conditions, including hypoxia, nutrient deprivation, and oxidative stress [28] This adaptive reprogramming involves deregulation of central metabolic pathways, including glycolysis, glutamine metabolism, lipid biosynthesis, and one-carbon metabolism, providing essential substrates for cell growth, such as ATP, biosynthetic intermediates, and reducing equivalents like NADPH.[29] Oncogenic mutations directly regulate metabolic pathways; for instance, MYC-driven tumours exhibit

enhanced glutaminolysis, while PI3K/AKT activation increases glucose uptake and glycolytic flux, indicating convergence between genetic and metabolic alterations.[30]

A critical advancement supporting the metabolic theory is the discovery of oncometabolites. Mutations in isocitrate dehydrogenase genes (IDH1 and IDH2) lead to 2-hydroxyglutarate accumulation, altering histone and DNA methylation, driving epigenetic reprogramming, and promoting tumorigenesis.[31] Similarly, fumarate and succinate accumulation inhibit prolyl hydroxylases, stabilizing hypoxia-inducible factors and promoting a pseudohypoxic state that enhances tumour progression. [32] Compared to the genetic model, the metabolic theory addresses several limitations. While genetic mutations are highly heterogeneous, metabolic reprogramming is remarkably conserved across cancers, with increased glucose uptake and lactate production observed in most tumours. [33] Restoring normal mitochondrial function can suppress tumorigenicity, suggesting that metabolic integrity may override genetic abnormalities.[34] However, the metabolic theory does not fully explain cancers driven by hereditary mutations, such as BRCA1/2-associated breast cancer, nor does it account for the specificity of certain oncogenic mutations. The genetic theory struggles to explain why diverse mutational profiles converge on similar metabolic phenotypes and why targeting single mutations often fails to produce durable clinical responses. [35] A critical synthesis suggests that cancer is a systems-level disease arising from dynamic interactions between genetic alterations and metabolic reprogramming. Genetic mutations rewire cellular metabolism, while metabolic dysregulation influences gene expression, epigenetic states, and genomic stability. [36] Metabolic intermediates regulate chromatin structure and gene transcription, linking metabolism to cellular identity and fate control. Integrating genetic and metabolic perspectives offers a comprehensive understanding of cancer biology, revealing potential therapeutic strategies that target metabolic vulnerabilities in conjunction with traditional genomic-based treatments. This multidimensional approach is essential for overcoming tumour heterogeneity, therapeutic resistance, and disease relapse, advancing precision oncology. [37]

Warburg Effect and Aerobic Glycolysis

A hallmark of cancer metabolism is the Warburg effect, a phenomenon first described by Otto Warburg, wherein tumour cells exhibit a predilection for aerobic glycolysis, converting glucose to lactate even in the presence of sufficient oxygen for oxidative phosphorylation. [38] In contrast to normal differentiated cells, which metabolize glucose through glycolysis to generate pyruvate, which is then oxidized through the tricarboxylic acid cycle and oxidative phosphorylation to produce approximately 34 molecules of ATP per glucose molecule, cancer cells exhibit a truncated glycolytic pathway, converting pyruvate to lactate via lactate dehydrogenase, yielding only two molecules of ATP per glucose molecule. This apparent energetic inefficiency is offset by the generation of metabolic intermediates required for biosynthetic pathways, including nucleotide, amino acid, and lipid synthesis, as well as the acidification of the tumour microenvironment, which facilitates tissue invasion and suppresses immune cell activity.[39] Furthermore, the Warburg effect is often accompanied by alterations in mitochondrial function, including reduced oxidative phosphorylation, increased reactive oxygen species production, and changes in mitochondrial dynamics, which contribute to the development of a tumour-promoting microenvironment.[40] The tumour microenvironment, comprising cancer-associated fibroblasts, immune cells, and endothelial cells, also plays a critical role in shaping cancer metabolism, modulating the expression of key metabolic enzymes, and influencing the availability of nutrients and growth factors.[41]

In glioblastoma, a highly aggressive brain cancer, inhibiting Aurora kinase A has been shown to reverse the Warburg effect, resulting in decreased glucose uptake and increased oxidative phosphorylation.[42] This shift in metabolic phenotype is associated with reduced tumor growth and improved survival, suggesting that targeting Aurora kinase A may be a promising therapeutic strategy for glioblastoma patients.[43] Interestingly, cancer-associated fibroblasts, a key component of the tumor microenvironment, exhibit aerobic glycolysis, promoting tumor growth and metastasis. This phenomenon, known as the reverse Warburg effect, highlights the complex interplay between cancer cells and their microenvironment. [44] In pancreatic cancer, researchers have found that inhibiting glycolysis using 3-bromopyruvate suppresses tumor growth and improves survival in a murine model.[45] This study suggests that targeting glycolysis may be an effective therapeutic approach for pancreatic cancer, a disease often characterized by poor prognosis and limited treatment options.

The Warburg effect also contributes to chemoresistance in cancer cells by upregulating glycolytic enzymes and increasing lactate production. This metabolic adaptation allows cancer cells to survive in the presence of chemotherapy, highlighting the need for novel therapeutic strategies that target cancer metabolism. Researchers are exploring various strategies to target the Warburg effect, including inhibiting glycolytic enzymes, modulating mitochondrial function, and exploiting metabolic vulnerabilities. For example, targeting hexokinase 2, a key enzyme involved in glycolysis, has been shown to inhibit tumor growth and improve survival in preclinical models.[46]

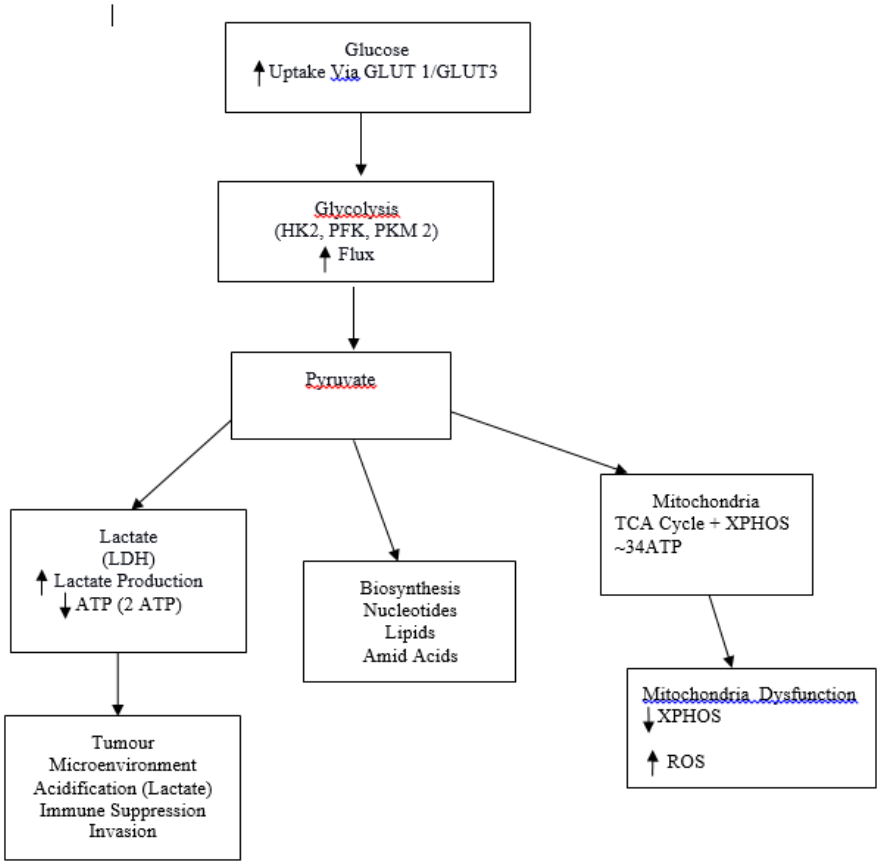

Figure 2: Schematic Diagram of Warburg Effect and Glycolytic Reprogramming

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Mitochondrial Dysfunction in Cancer

Mitochondrial dysfunction is a fundamental component of cancer metabolism, underpinning the malignant phenotype through perturbations in energy production, reactive oxygen species (ROS) generation, and regulation of programmed cell death. [47] The integrity of mitochondrial function is critical for maintaining cellular homeostasis, and defects in mitochondrial respiration compromise the efficiency of oxidative phosphorylation, thereby promoting a reliance on glycolytic metabolism. Concomitantly, impaired mitochondrial function is associated with increased production of ROS, highly reactive molecules capable of inducing DNA damage, protein oxidation, and lipid peroxidation, ultimately contributing to genomic instability and tumorigenesis.[48] The causal link between mitochondrial dysfunction and cancer is underscored by nuclear-cytoplasmic transfer studies, wherein the introduction of a nucleus from a tumour cell into a cytoplasm containing normal mitochondria results in suppression of the tumorigenic phenotype, despite the presence of oncogenic mutations in the nucleus.[49] This observation highlights the critical role of mitochondrial integrity in controlling malignant transformation. Furthermore, the tumour microenvironment, characterized by hypoxia, nutrient deprivation, and oxidative stress, exacerbates mitochondrial dysfunction, creating a self-reinforcing cycle that drives cancer progression.[50] Tumor Suppressor p53, a tumor suppressor protein, regulates mitochondrial function and promotes oxidative phosphorylation.[51] Mutations in p53 lead to impaired mitochondrial function and increased glycolysis.[52]

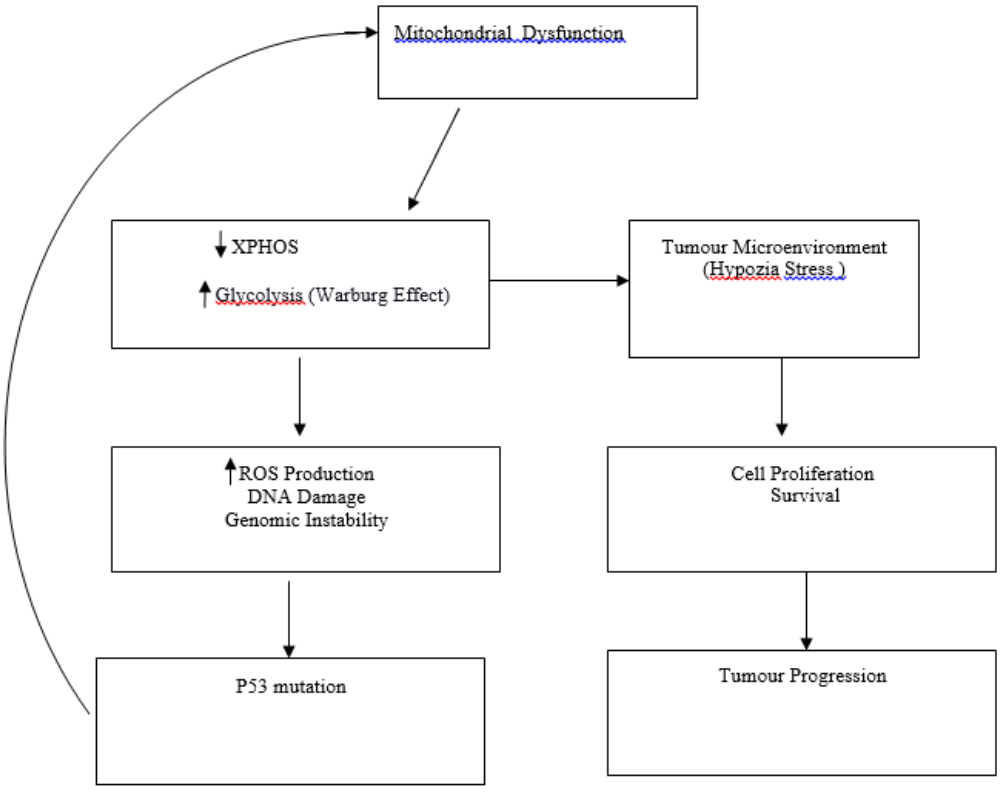

Figure 3: Schematic Diagram of Mitochondrial Dysfunction in Tumour Progesson

Oncometabolites and Epigenetic Regulation

A growing body of evidence has identified specific metabolites, known as oncometabolites, which accumulate abnormally in tumour cells and actively promote oncogenesis through epigenetic reprogramming.[53] For instance, 2-hydroxyglutarate, a metabolite that accumulates in certain brain tumours due to mutations in isocitrate dehydrogenase enzymes, inhibits α-ketoglutarate-dependent dioxygenases involved in histone and DNA demethylation, leading to aberrant epigenetic modifications and altered gene expression patterns that promote tumorigenesis [54] Other oncometabolites, including fumarate, sarcosine, glycine, asparagine, and choline, participate in metabolic networks that influence tumour growth, metastasis, and cellular differentiation, underscoring the complex interplay between metabolic dysregulation and epigenetic reprogramming in cancer.[55]

The dysregulation of mitochondrial function and the accumulation of oncometabolites also have profound implications for cancer therapy, as they can modulate the tumour microenvironment, influence immune responses, and impact the efficacy of therapeutic interventions. [56] Elucidating the intricate relationships between mitochondrial dysfunction, oncometabolites, and epigenetic regulation is essential for the development of novel therapeutic strategies that target the metabolic vulnerabilities of cancer cells. The oncometabolites 2-hydroxyglutarate, fumarate, and succinate are key players in driving cancer development and progression. 2-Hydroxyglutarate, produced by mutant isocitrate dehydrogenase enzymes, competitively inhibits α-ketoglutarate-dependent dioxygenases, leading to aberrant epigenetic modifications and altered gene expression patterns. [57] This inhibition disrupts normal cellular processes, promoting tumorigenesis. Fumarate and succinate, on the other hand, inhibit prolyl hydroxylase domain enzymes, stabilizing hypoxia-inducible factor and promoting angiogenesis and tumorigenesis. [58] Elevated levels of sarcosine contribute to prostate cancer progression by promoting epithelial-to-mesenchymal transition and modulating androgen receptor activity, highlighting the complex interplay between metabolic dysregulation and cancer development.[59] These oncometabolites create a permissive environment for tumour growth and metastasis, underscoring their potential as therapeutic targets in cancer treatment.[60]

Metabolic Reprogramming of Glucose Utilization

Cancer cells display markedly increased glucose uptake, driven by the overexpression of glucose transporters like GLUT1 and GLUT3 [61]. This heightened glucose uptake supports their elevated glycolytic rates, enabling cancer cells to meet energy and biosynthetic needs. Once internalized, glucose is rapidly metabolized through the concerted action of key glycolytic enzymes, including hexokinase 2, which catalyzes the phosphorylation of glucose to glucose-6-phosphate, thereby effectively sequestering glucose within the cell. Phosphofructokinase, a major regulatory enzyme, governs glycolytic flux, while pyruvate kinase isoform M2 plays a pivotal role in directing glycolytic intermediates toward anabolic pathways, facilitating macromolecule synthesis.[62]

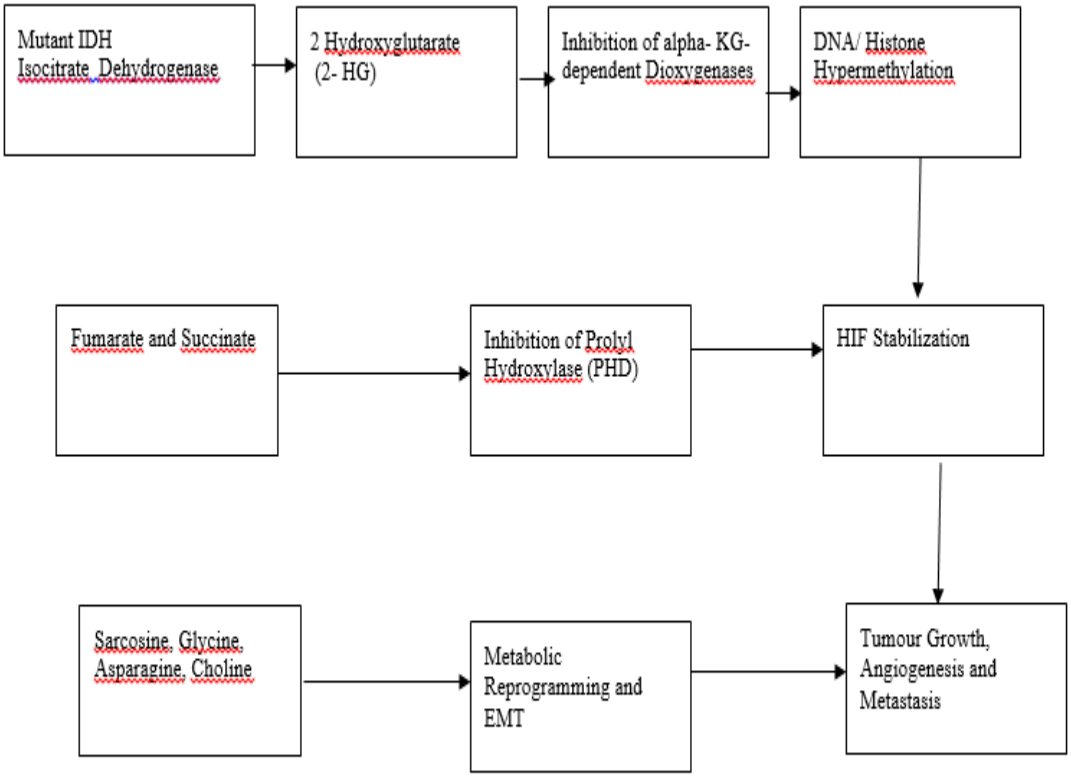

Figure 4: Schematic Diagram of Oncometabolite Pathways and Epigenetic Regulation

Hypoxia and Hypoxia Inducible Factor Signalling

The tumour microenvironment, characterized by hypoxic regions, exerts a profound influence on glucose metabolism. Hypoxia triggers the stabilization of hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α, which are normally targeted for proteasomal degradation under normoxic conditions through the action of prolyl hydroxylase domain enzymes and the von Hippel-Lindau protein.[63] However, under hypoxic conditions, HIFs accumulate in the nucleus, where they activate the transcription of genes involved in glycolysis, angiogenesis, and cellular survival, thereby promoting a metabolic shift toward aerobic glycolysis. [64] This adaptive response enables cancer cells to survive and proliferate in the face of adverse environmental conditions. Furthermore, HIFs also modulate the expression of genes involved in mitochondrial biogenesis and function, contributing to the suppression of oxidative phosphorylation and the promotion of glycolytic metabolism. [65] The interplay between HIFs, glucose metabolism, and mitochondrial function underscores the complex regulatory networks that govern cancer metabolism, highlighting the need for a comprehensive understanding of these processes to develop effective therapeutic strategies.

Oncogenic Signalling Pathways in Metabolic Reprogramming

Oncogenic signalling pathways play a pivotal role in orchestrating the metabolic reprogramming of cancer cells, enabling them to sustain their elevated energy demands and biosynthetic requirements. The

phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT) pathway is a key regulator of cancer metabolism, augmenting glucose uptake, stimulating glycolytic enzyme expression, and promoting anabolic metabolism. [66] This pathway is often activated in breast cancer, contributing to poor prognosis and resistance to therapy, and PI3K inhibitors like alpelisib are being explored as therapeutic options. The MYC transcription factor complements this process by regulating genes involved in ribosome biogenesis, nucleotide synthesis, glycolysis, and glutamine metabolism, thereby conferring metabolic flexibility to tumour cells.[67] MYC also promotes mitochondrial biogenesis and function, supporting the energy demands of rapidly proliferating cancer cells, and is a key driver of lymphoma development and progression. Targeting MYC using BET inhibitors like JQ1 has shown promise in preclinical models.[68] Glycolytic enzymes, such as PKM2, are upregulated in various cancers. Targeting PKM2 inhibits cancer cell growth and induces apoptosis, highlighting the potential therapeutic opportunities for targeting cancer metabolism.[69]

Glutamine Metabolism and Glutamine Addiction

Glutamine metabolism is a critical component of cancer cell metabolism, with many tumour cells exhibiting a pronounced reliance on glutamine as a metabolic substrate, a phenomenon often referred to as glutamine addiction. Glutamine serves as a vital source of carbon and nitrogen atoms for the biosynthesis of nucleotides, amino acids, and other macromolecules. The uptake of glutamine is mediated by several membrane transporters, including SLC1A5, SLC7A5, SLC38A1, and SLC38A2, and is subsequently converted to glutamate through the action of glutaminase.[70] Glutamate is then converted to α-ketoglutarate by glutamate dehydrogenase, an intermediate that enters the tricarboxylic acid cycle, contributing to energy production and biosynthetic reactions.[71]

Lipid Metabolism in Cancer

Lipid metabolism is also profoundly altered in cancer cells, with rapidly proliferating tumour cells requiring large quantities of lipids for membrane synthesis, energy storage, and signal transduction.[72] To meet these demands, cancer cells activate pathways responsible for de novo lipid synthesis and uptake of extracellular fatty acids. De novo lipogenesis involves the conversion of acetyl-CoA into fatty acids, a process regulated by key enzymes including ATP citrate lyase, acetyl-CoA carboxylase, and fatty acid synthase. Stearoyl-CoA desaturase introduces double bonds into fatty acid chains, producing unsaturated lipids required for membrane fluidity. The transcription factor sterol regulatory element-binding protein (SREBP) governs the expression of these enzymes. Cancer cells also import fatty acids via membrane proteins like CD36, fatty acid transport proteins, and fatty acid-binding proteins. These fatty acids undergo β-oxidation, producing acetyl-CoA, NADH, and $FADH_2$, which feed into mitochondrial energy metabolism. [73] The tumour microenvironment, including cancer-associated fibroblasts and immune cells, also plays a critical role in shaping lipid metabolism, influencing the expression of key enzymes and modulating the availability of lipids and growth factors. [74] Furthermore, the interplay between lipid metabolism and other metabolic pathways, such as glucose and glutamine metabolism, underscores the complex regulatory networks that govern cancer metabolism, highlighting the need for a comprehensive understanding of these processes to develop effective therapeutic strategies

Tumour Markers and Metabolic Biomarkers

Tumour markers and metabolic biomarkers play a pivotal role in the diagnosis, prognosis, and treatment monitoring of cancer. [75]These biomolecules, produced either directly by tumour cells or by host tissues

in response to malignant growth, can be detected in biological fluids, including blood, urine, and saliva, or within tumour tissues themselves. Serum tumour markers, such as prostate-specific antigen for prostate cancer, alpha-fetoprotein for hepatocellular carcinoma, and carcinoembryonic antigen for colorectal cancer, are widely used in clinical practice [75]. Tissue-based markers, including hormone receptors in breast cancer and leukocyte surface antigens in hematological malignancies, provide valuable information for treatment decision-making. [76] Metabolic biomarkers, such as lactate, serine, sarcosine, and choline, reflect altered tumour metabolism and have garnered increasing attention for their potential in non-invasive screening and early diagnosis of certain cancers.[77] The detection of these metabolites may enable the identification of patients at high risk of developing cancer or those with early-stage disease, thereby improving treatment outcomes.

Cancer-Associated Cachexia

Cancer-associated cachexia is a complex metabolic disorder characterized by progressive weight loss, skeletal muscle wasting, adipose tissue depletion, and elevated energy expenditure.[77,78] Chronic inflammation plays a central role in the pathogenesis of cachexia, with proinflammatory cytokines, including tumour necrosis factor-alpha, interleukin-1, and interleukin-6, stimulating catabolic pathways that accelerate the breakdown of muscle proteins and adipose tissue.[78]These cytokines also alter hypothalamic signalling pathways, leading to reduced appetite and increased metabolic rate. Alterations in carbohydrate metabolism are common in cachectic patients, with tumour cells consuming large quantities of glucose through glycolysis, while the liver increases gluconeogenesis to maintain blood glucose levels.[79] The Cori cycle, a futile metabolic cycle, consumes large amounts of energy and contributes to systemic metabolic inefficiency. Lipid metabolism undergoes significant alterations, marked by enhanced adipose tissue lipolysis that releases fatty acids into circulation. Concurrently, white adipose tissue undergoes browning, characterized by uncoupling protein-1 expression and increased mitochondrial density.

Muscle wasting represents another hallmark of cancer cachexia, with the activation of transcription factors, such as nuclear factor kappa-B and forkhead box O, inducing the expression of genes involved in the ubiquitin-proteasome pathway, a major system responsible for protein degradation in skeletal muscle. [80,81] Myostatin signalling further inhibits muscle growth, exacerbating muscle atrophy.

Systemic Metabolic Dysfunction in Cancer

The interplay between tumour cells, the tumour microenvironment, and systemic metabolism underscores the complexity of cancer cachexia, highlighting the need for a comprehensive understanding of these processes to develop effective therapeutic strategies. The identification of novel biomarkers and therapeutic targets, including those involved in metabolic reprogramming, may provide new opportunities for the diagnosis, treatment, and prevention of cancer cachexia. The systemic repercussions of cancer extend far beyond the confines of the tumour itself, precipitating a profound perturbation of whole-body physiology. Multiple organs, including the liver, adipose tissue, skeletal muscle, and central nervous system, are recruited into a complex network of metabolic dysregulation.[82] Hepatic metabolism is reprogrammed, characterized by augmented gluconeogenesis, enhanced production of acute-phase proteins, and the development of hepatic steatosis. Concomitantly, neuroendocrine changes, mediated by hormones such as cortisol, epinephrine, and norepinephrine, further disrupt energy homeostasis, underscoring the multifaceted nature of cancer's systemic metabolic effects. [83]The recognition that metabolic

reprogramming is a fundamental hallmark of cancer biology has profound implications for our understanding of tumourigenesis and the development of novel therapeutic strategies. Tumour cells exploit glucose, amino acid, and lipid metabolism to sustain rapid proliferation and survive within hostile microenvironments, driven by complex interactions between genetic mutations, mitochondrial dysfunction, and oncogenic signalling pathways. Elucidation of these metabolic mechanisms provides a rich source of opportunities for the development of diagnostic biomarkers and targeted therapeutic interventions. Interventions aimed at inhibiting glycolysis, glutaminolysis, or lipid synthesis are currently being explored as potential treatments, while metabolic biomarkers may enable earlier detection of cancer and more precise monitoring of treatment responses. The integration of metabolic insights with genomic and immunological approaches is poised to revolutionize our understanding of cancer biology, ultimately leading to more effective strategies for preventing and treating this complex disease.

Conclusion

The emerging field of cancer metabolism holds promise for the development of novel therapeutic strategies, including the targeting of specific metabolic pathways, such as the PI3K/AKT/mTOR axis, and the exploitation of metabolic vulnerabilities, such as the Warburg effect. Additionally, the identification of metabolic biomarkers, including those involved in glucose, amino acid, and lipid metabolism, may enable the early detection of cancer and the monitoring of treatment responses. Ultimately, a deeper understanding of the complex interplay between cancer cells, the tumour microenvironment, and systemic metabolism will be essential for the development of effective therapeutic strategies aimed at preventing and treating cancer.

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