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Unravelling the pathways driving tumour growth and resistance

Metabolic Reprogramming in Cancer

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Abstract

Background: Cancer is a complex and adaptive disease characterised by uncontrolled cell proliferation, tissue invasion, and metastasis. Previously thought to be a genetic disease caused by DNA abnormalities, recent research demonstrates the critical role of metabolic reprogramming in cancer development. Cancer cells experience severe metabolic changes in the tumour microenvironment (TME), which include nutritional deprivation, hypoxia, and low pH.

Main text: The Warburg effect is a dramatic shift in which cells rely on aerobic glycolysis instead of oxidative phosphorylation (OXPHOS) for rapid energy production and growth. MYC, an oncogene, and TP53, a tumour suppressor, regulate metabolic alterations by increasing glycolysis, glutaminolysis, and other pathways necessary for tumour survival. Mitochondrial failure causes genomic instability, cancer, and resistance to apoptosis, increasing reliance on glycolysis and glutaminolysis. Cancer stem cells (CSCs) and resistant tumour forms are metabolically flexible, allowing them to adapt to environmental changes. The TME regulates metabolic pathways that promote tumour growth, including HIFs and AMPK.

Conclusion: Therapeutic drugs that target altered metabolic pathways, such as glycolytic enzyme inhibitors, glutaminolysis, and mitochondrial function, have shown promise in both preclinical and clinical studies. However, the metabolic flexibility of cancer cells and tumour heterogeneity make treatment problematic. Recent therapeutic strategies combining metabolic inhibitors, chemotherapy, and immunotherapy have yielded promising results.

Keywords: Metabolic Reprogramming, Warburg Effect, Tumour Microenvironment (TME), Oncogenes, Glycolysis, Mitochondrial Dysfunction, Cancer Stem Cells (CSCs), Therapeutic Strategies

Background

Cancer is a complex disease characterised by uncontrolled cell growth, tissue invasion, and the ability to spread to distant organs (1). Its treatment remains challenging due to its adaptability, the complexity of its mechanisms, and the development of resistance to therapies. Cancer can arise from various triggers, including environmental factors such as radiation, chemicals, and inflammation (2). Despite significant research, the origins and precise mechanisms of cancer remain elusive, posing an ongoing challenge in understanding the disease fully.

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Metabolic alterations in cancer cells are central to tumorigenesis and cancer progression. These metabolic changes enable cancer cells to thrive under the harsh conditions of the tumour microenvironment (TME), such as nutrient deprivation, hypoxia, and low pH (3). The Warburg effect, where cancer cells exhibit enhanced glycolysis even in oxygen, is a well-known metabolic hallmark (4). Recent research has revealed that these metabolic shifts are not merely due to damaged cellular respiration but are driven by genetic mutations, oncogenes, tumour suppressors, and interactions with the TME (5).

These metabolic alterations support rapid tumour cell proliferation and survival. Cancer cells exploit various metabolic pathways, including glycolysis, oxidative phosphorylation (OXPHOS), glutaminolysis, lipid metabolism, and amino acid metabolism, to maintain growth (6). Oncogenes like MYC and RAS drive anabolic processes, enhancing nutrient uptake for biosynthesis and tumour growth (7). Additionally, the loss of tumour suppressors like TP53 and LKB1 further accelerates these metabolic shifts, allowing cancer cells to evade growth suppression and resist cell death (8).

The TME plays a key role in shaping cancer cell metabolism. Factors such as hypoxia, nutrient limitations, and waste accumulation induce metabolic adaptations favouring anaerobic glycolysis and other pathways essential for cell survival (9). Hypoxia-inducible factors (HIFs) regulate glycolytic enzymes in response to low oxygen, while pathways like AMP-activated protein kinase (AMPK) and mTOR signalling balance energy supply and demand (10). Targeting these metabolic pathways has emerged as a promising therapeutic strategy, with research focused on inhibiting enzymes involved in glycolysis, OXPHOS, and other critical metabolic processes to disrupt cancer cell metabolism and improve patient outcomes.

Methods

A comprehensive search was conducted across several scientific databases, including PubMed, Google Scholar, Web of Science, Scopus, Embase, and ClinicalTrials.gov, to gather peer-reviewed articles, reviews, meta-analyses, and clinical trial data. Keywords such as "cancer metabolism," "Warburg effect," "glycolysis," "mitochondrial dysfunction," and "therapeutic targeting" were used to identify relevant studies. The inclusion criteria focused on articles that discussed metabolic shifts in cancer, such as glycolysis, glutaminolysis, and oxidative phosphorylation, and the role of key oncogenes, tumour suppressors, and metabolic pathways in cancer progression and resistance to therapies. Studies addressing preclinical and clinical trials targeting metabolic inhibitors, as well as those exploring the interactions between the tumour microenvironment (TME) and cancer cell metabolism, were prioritised. Articles lacking scientific rigour or not directly related to metabolic reprogramming were excluded. Data extraction focused on study design, key findings, therapeutic approaches, clinical relevance, the impact of TME, and the role of epigenetic regulation in cancer metabolism. The extracted data were analysed qualitatively to identify metabolic pathways and therapeutic targets, particularly those involved in glycolysis, mitochondrial function, and metabolic intermediates.

Main text

Cancer as a Metabolic Disease

Cancer has traditionally been seen as a genetic disease, driven by mutations in DNA that lead to uncontrolled cell growth and metastasis. However, recent research suggests that cancer can also be fundamentally linked to disruptions in cellular energy metabolism (11). This shift in perspective highlights that cancer cells undergo significant metabolic alterations to support their growth and survival in hostile environments. One of the most notable metabolic changes in cancer cells is the reliance on substrate-level phosphorylation rather than oxidative phosphorylation (OXPHOS) to generate energy (12). This shift is central to cancer progression and contributes to several hallmarks of malignancy, such as genomic instability. The Warburg effect, a hallmark of aerobic glycolysis, exemplifies this metabolic alteration, where cancer cells prefer glycolysis even in the presence of oxygen, further supporting the idea that altered metabolism is crucial to cancer development (13). These metabolic changes in cancer cells not only facilitate tumour initiation but also contribute to cancer's growth and spread. This growing body of evidence suggests that cancer may be better understood as a metabolic disease, with cellular metabolism playing a pivotal role in cancer's onset, progression, and malignancy, alongside genetic factors.

The Hallmarks of Cancer

Researchers Hanahan and Weinberg identified six hallmarks of cancer that underlie nearly all types of cancer: self-sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and the ability to invade tissues and metastasise (14). Self-sufficiency in growth signals allows cancer cells to produce or become insensitive to growth signals, enabling

uncontrolled proliferation. Insensitivity to growth-inhibitory signals further promotes this unchecked growth. The evasion of apoptosis enables damaged or mutated cells to survive and continue dividing, while limitless replicative potential allows cancer cells to bypass normal cellular ageing mechanisms. Sustained angiogenesis ensures a constant blood supply to tumours, supporting their growth, and the ability to invade tissues and metastasise contributes to the aggressiveness of cancer. Alongside these hallmarks, genomic instability—an increased mutation rate—is a key feature of cancer cells, although the idea that genomic mutations alone drive cancer has been questioned (15). Many mutations occur too infrequently to fully explain cancer's rapid progression, suggesting the need to explore other contributing factors.

Emerging perspectives challenge the idea that cancer is primarily a genetic disease, proposing instead that it could be a metabolic disease. Mitochondrial dysfunction is considered a central driver of cancer, as impaired cellular respiration and energy metabolism may trigger genetic instability, contributing to the hallmark features of cancer (16). This metabolic defect is thought to potentially initiate cancer, rather than genetic mutations alone (17). The loss of "genomic caretakers," proteins involved in DNA repair, further exacerbates genomic instability, allowing mutations to accumulate and driving tumour progression (18). This shift in understanding emphasises the importance of focusing on mitochondrial dysfunction and metabolic reprogramming as key contributors to tumorigenesis.

Altered Metabolism in Cancer

Cancer cells undergo significant metabolic reprogramming to support rapid growth and survival in the tumour microenvironment. One key metabolic alteration is the shift from oxidative phosphorylation (OXPHOS) to aerobic glycolysis, known as the Warburg effect (19). This shift occurs even in sufficient oxygen, where cancer cells preferentially rely on glycolysis for energy production rather than the more efficient OXPHOS process. In addition to glycolysis, cancer cells exhibit a heavy dependence on glutamine, which is crucial for anaplerosis (replenishing metabolic intermediates) and biosynthesis (20). Glutamine provides essential precursors for nucleotides, amino acids, and lipids, thereby supporting the proliferation and survival of cancer cells. Furthermore, cancer cells show increased lipogenesis for membrane biosynthesis during cell division and reprogrammed fatty acid oxidation to better support energy production and biomass accumulation (21). These metabolic changes are fundamental in enabling cancer cells to maintain rapid growth and adapt to the stresses of the tumour microenvironment.

Genetic mutations in oncogenes and tumour suppressor genes are major drivers of these metabolic alterations. Oncogenes such as MYC and mutant tumour suppressors like TP53 play central roles in reprogramming metabolic pathways, helping tumour cells meet the high metabolic demands of uncontrolled proliferation and resistance to cell death (22). These mutations enable cancer cells to thrive in harsh conditions, making them more aggressive and resistant to treatments (23).

Mechanisms Driving the Warburg Effect

The Warburg effect, a hallmark of cancer metabolism, involves a shift from oxidative phosphorylation (OXPHOS) to glycolysis, even in the presence of oxygen. Cancer cells preferentially convert glucose into pyruvate, which is then converted into lactate, a process known as aerobic glycolysis. This metabolic alteration enables cancer cells to efficiently produce energy and biomass, supporting their rapid proliferation (24). Accompanying this shift is increased glucose uptake, upregulated glycolytic enzymes, and higher glycolytic flux, all of which contribute to the uncontrolled proliferation of cancer cells. The Warburg effect is regulated by various genetic and regulatory factors, notably the transcription factor HIF-1α, which is activated under low oxygen conditions (25). HIF-1α upregulates key glycolytic enzymes such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA), facilitating glucose conversion into lactate and reinforcing the metabolic shift (26). Additionally, the oncogene c-Myc collaborates with HIF-1α to enhance the transcription of glycolytic genes, further promoting glucose uptake and lactate production, which drives the Warburg effect in cancer cells (27).

The Warburg effect is actively influenced by genetic mutations in oncogenes and tumour suppressor genes (28). For instance, the tumour suppressor p53 normally inhibits glycolysis, and its loss leads to increased glycolytic activity, supporting the Warburg effect and promoting cancer cell survival and proliferation (29). Recent research, including lipidomic and proteomic studies, has provided further evidence of mitochondrial dysfunction contributing to the Warburg effect. These studies show that cancer cells often exhibit a decreased b-F1-ATPase/Hsp60 ratio and upregulation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), indicating that cancer cells rely more on substrate-level phosphorylation than normal cells (30). This reliance on glycolysis, driven by

compromised mitochondrial oxidative phosphorylation, ensures that cancer cells maintain energy production, even when mitochondrial function is reduced. This shift in energy production is critical for cancer cell survival, enabling them to continue proliferating under adverse conditions, where other metabolic pathways might be compromised.

Role of Tumour Suppressors in Glycolytic Phenotype

Oncogenes and tumour suppressors play crucial roles in regulating mitochondrial function and oxidative phosphorylation (OXPHOS), impacting cancer metabolism. For instance, c-Myc, an oncogene, stimulates mitochondrial biogenesis and respiration, promoting rapid cell growth (31). In contrast, p53, a tumour suppressor, regulates cellular metabolism by inhibiting glycolysis and promoting OXPHOS, particularly through the activation of TP53-induced glycolysis and apoptosis regulator (TIGAR), which shifts metabolism toward the pentose phosphate pathway (32). This shift enhances antioxidant defence, protecting cells against oxidative stress and DNA damage. When p53 is mutated, however, it disrupts mitochondrial function and leads to a reprogrammed metabolic state that favours cancer progression (33). The alterations in the regulation of OXPHOS, driven by these genetic changes, contribute to tumorigenesis and the complexity of metabolic reprogramming in cancer cells (34). Tumour suppressors, like p53, typically act to suppress glycolysis and maintain cellular homeostasis, but their loss can lead to enhanced glycolysis, exacerbating the Warburg effect, a hallmark of cancer metabolism.

Oncogenes such as MYC, when activated, promote glycolysis, glutaminolysis, and lipid synthesis, which are crucial for tumour growth and survival (35). These metabolic alterations are driven by oncogenic signalling pathways like PI3K/Akt/mTOR, which enhance glycolysis and nutrient uptake (36). MYC's activation supports metabolic reprogramming through increased glutamine metabolism and biosynthesis, contributing to the aggressive growth and metastasis of cancer cells (37). In cancers where p53 is lost or mutated, the glycolytic phenotype is upregulated, further supporting the Warburg effect, which allows cells to bypass mitochondrial dysfunction by relying on the less efficient but faster process of glycolysis. This adaptation helps cancer cells maintain ATP production despite mitochondrial damage.

Impact of Mitochondrial Dysfunction and Metabolic Reprogramming in Cancer Progression and Therapy Resistance

Telomerase, a ribonucleoprotein complex crucial for maintaining telomere integrity and enabling unlimited cell replication, is highly active during early embryonic development, correlating with anaerobic glycolysis and rapid cell proliferation. In adult tissues, however, telomerase activity is suppressed as energy production shifts toward oxidative phosphorylation (OXPHOS). Recent evidence suggests that mitochondrial dysfunction may lead to the relocation of telomerase from mitochondria, where it has a protective role, to the nucleus, where it plays a critical role in maintaining telomere integrity (38). The exact relationship between telomerase and mitochondrial function remains unclear, but this mechanism could be key to sustaining the replicative potential of tumour cells, highlighting its potential involvement in the metabolic reprogramming associated with cancer progression. Mitochondrial dysfunction, a hallmark of cancer cells, forces cells to rely on glycolysis and glutaminolysis for energy production rather than OXPHOS (39). Disruptions in mitochondrial membranes, especially cardiolipin, result in decreased proton motive force, mitochondrial uncoupling, and reduced ATP production, contributing to genomic instability and cellular dysfunction (40). This dysfunction also impacts tumour suppressor genes like p53, which helps maintain genome integrity through cell cycle arrest and apoptosis (41). When mitochondria are impaired, p53's function is compromised, weakening its ability to control cell proliferation and preventing tumour formation. Furthermore, mitochondrial dysfunction activates oncogenes such as MYC and RAS, which drive metabolic reprogramming, promoting glycolysis and survival pathways that support tumour growth and resistance to normal growth control (42).

Cancer cells, particularly in resistant forms like acute myeloid leukaemia (AML), exhibit dual reliance on glycolysis and OXPHOS, enabling them to adapt to fluctuating oxygen and nutrient levels, essential for survival (43). This metabolic flexibility allows cancer cells to evade therapy, making them more resilient to treatment. Targeting glycolysis and OXPHOS presents a potential strategy to overcome this metabolic flexibility, making resistant cancer cells more vulnerable to treatment. Mitochondrial dynamics, such as fission and fusion, regulated by proteins like Drp1 and Mfn1/2, play a crucial role in optimising OXPHOS efficiency to meet the energy demands of rapidly dividing cancer cells (44). Additionally, the activation of PGC-1α, a regulator of mitochondrial biogenesis, boosts mitochondrial function and supports the increased energetic demands of cancer cells, ensuring their survival and proliferation even in

adverse conditions (45). These mitochondrial adaptations are critical to the uncontrolled growth and metabolic reprogramming of cancer cells, further promoting their progression and resistance to therapy.

Role of Mitochondrial Dysfunction in Chromosomal Instability, Cancer Progression, and Metastasis Mitochondrial dysfunction plays a critical role in driving chromosomal instability and cancer progression by disrupting calcium homeostasis, impairing mitosis, and causing chromosome segregation defects, leading to aneuploidy and chromosomal rearrangements. Mitochondrial damage also affects mitochondrial DNA (mtDNA), impairing DNA repair enzymes and promoting mutagenesis (46). This combination of defective mitochondrial function, compromised DNA repair, and increased reactive oxygen species (ROS) production accelerates the mutator phenotype, characterised by high mutation rates that drive cancer development (47). Additionally, mitochondrial dysfunction is a key factor in the evasion of apoptosis in cancer cells. Normally, mitochondrial damage triggers an apoptotic cascade through the release of cytochrome c and the activation of caspases, leading to cell death. However, cancer cells bypass apoptosis through a shift from mitochondrial respiration to glycolysis and substrate-level phosphorylation, supported by several signalling pathways, including mTOR, MYC, Ras, HIF-1α, and IGF-1/PI3K/Akt (48). These pathways not only regulate glycolysis but also inhibit p53, a major mediator of apoptosis, enabling cancer cells to survive and proliferate despite cellular stress. Furthermore, angiogenesis, essential for tumour growth, is closely tied to metabolic reprogramming in cancer cells (49). Hypoxia-inducible factor 1-alpha (HIF-1α) is activated under low oxygen conditions and promotes both glycolysis and the expression of vascular endothelial growth factor (VEGF), crucial for new blood vessel formation (50). The IGF-1/PI3K/Akt pathway further enhances vascularity, ensuring continued tumour survival and expansion.

The spread of cancer through metastasis involves multiple complex steps, including detachment, intravasation, evasion of immune surveillance, extravasation, and proliferation at distant sites. Metastatic potential is influenced by metabolic changes, particularly mitochondrial dysfunction, which forces tumour cells to rely on substrate-level phosphorylation for energy production. Studies show that cancer cells may acquire macrophage-like properties, enabling migration, extracellular matrix degradation, and survival in hypoxic environments—all necessary for metastasis (51). This macrophage-like behaviour is linked to the RTG (retrograde) response triggered by mitochondrial damage. Metastatic cancer cells also exhibit a robust Warburg effect, similar to primary tumour cells, suggesting that metabolic dysfunction not only characterises the primary tumour but also contributes to metastatic spread (52). Over time, the progressive shift from normal cellular metabolism to reliance on glycolysis and alternative energy pathways, driven by mitochondrial dysfunction, leads to DNA damage, genomic instability, and the activation of oncogenes while inactivating tumour suppressor genes (53). The RTG response further exacerbates this instability by linking mitochondrial dysfunction to genomic instability through changes in nuclear gene expression and activation of energy-saving mechanisms like glycolysis and glutaminolysis (54). In mammalian cells, prolonged RTG activation contributes to chromosomal instability, driving mutations in key genes that fuel cancer development. At moderate levels, ROS act as signalling molecules that promote metastatic behaviours, such as cell migration and invasion. ROS activate pro-metastatic pathways, including NF-κB, MAPK, and PI3K-Akt, which regulate crucial processes like cell proliferation, survival, and migration, thereby contributing to cancer progression and metastasis (55). Drugs targeting Complex I of the mitochondrial electron transport chain, such as metformin and IACS-010759, have shown promising results in preclinical studies, suggesting that modulating OXPHOS could be effective in hindering tumour growth and survival under adverse conditions (56).

Targeting Metabolic Pathways in Cancer Therapy: Glycolysis, TCA Cycle, and Lipid Metabolism

Cancer cells exhibit significant metabolic alterations, particularly a shift to aerobic glycolysis, which provides opportunities for therapeutic targeting. The upregulation of glycolytic enzymes and the reliance on specific metabolic pathways make cancer cells highly dependent on glycolysis for energy production. Inhibiting glycolytic enzymes or blocking glutamine metabolism can disrupt these energy pathways, limiting the growth of cancer cells. Drugs like 3-PO and koningic acid inhibit glycolysis by accumulating lactic acid or inhibiting enzymes like glyceraldehyde-3-phosphate dehydrogenase (GAPDH), while lactate dehydrogenase (LDH) inhibitors such as galloflavin and FX11 prevent the conversion of pyruvate to lactate, further hindering glycolysis (57). These inhibitors induce metabolic stress in cancer cells, offering potential therapeutic strategies, particularly for tumours exhibiting the

Warburg effect, where glycolysis predominates even when oxygen is available. Targeting glycolysis, through enzymes or glucose transporters like GLUT1, could significantly limit glucose availability, hindering tumour growth and enhancing the effectiveness of traditional therapies like chemotherapy or immunotherapy (58).

The tricarboxylic acid (TCA) cycle also presents a valuable target in cancer therapy due to its frequent dysregulation in tumours. Mutations in TCA cycle enzymes like succinate dehydrogenase (SDH), fumarase (FH), and isocitrate dehydrogenase (IDH) often lead to the accumulation of metabolites such as succinate and fumarate, which stabilise hypoxia-inducible factors (HIFs) and contribute to tumorigenesis. Targeting these metabolic disruptions, particularly through HIF inhibitors, could exploit cancer cell vulnerabilities (59). Additionally, mutations in IDH enzymes, which lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), promote tumorigenesis and create opportunities for targeted therapy. IDH inhibitors like ivosidenib and enasidenib have shown effectiveness in treating cancers with IDH mutations, such as gliomas and acute myeloid leukaemia (60). Combining TCA cycle inhibitors or IDH-targeted therapies with chemotherapy or immunotherapy could enhance the therapeutic efficacy by addressing multiple metabolic vulnerabilities in cancer cells (61).

Lipid metabolism also plays a crucial role in cancer cell growth and survival, and targeting lipid biosynthesis offers a promising therapeutic avenue. Enzymes like fatty acid synthase (FASN) and acyl-CoA synthetase (ACSL) are key regulators of lipid metabolism, and inhibiting these enzymes can disrupt tumour growth (62). Emerging therapies that target lipid biosynthesis have demonstrated potential in preclinical models, although further research is needed to optimise these strategies. Additionally, IDH mutations lead to altered lipid metabolism, which can be exploited through inhibitors targeting lipid synthesis or fatty acid oxidation, further broadening the scope for therapeutic intervention. Overall, targeting key metabolic pathways like glycolysis, TCA cycle enzymes, and lipid metabolism, combined with traditional cancer therapies, could offer new opportunities to disrupt the metabolic reprogramming that supports tumour growth and resistance, improving treatment outcomes for cancer patients (63).

Targeting Glutamine Metabolism in Cancer Therapy: Strategies and Opportunities

Glutamine metabolism plays a crucial role in the energy production and biosynthesis of cancer cells, particularly in hematopoietic and myeloid tumours. Cancer cells heavily rely on glutamine to fuel the tricarboxylic acid (TCA) cycle, converting glutamine into glutamate and subsequently into α-ketoglutarate, a vital metabolite in the cycle (64). This process is essential for sustaining cell growth and proliferation. Additionally, glutamine metabolism supports glycolysis by replenishing TCA cycle intermediates, thus contributing to the Warburg effect, a metabolic shift often observed in cancer cells. This glutamine dependency highlights the importance of targeting glutamine metabolism as a promising therapeutic strategy to disrupt tumour growth and survival.

Several therapies targeting glutamine metabolism have been explored, including phenylacetate and DON (6-diazo-5-oxo-l-norleucine), which aim to inhibit key enzymes in the glutamine metabolic pathway (65). However, these therapies face challenges such as toxicity and limiting their widespread use. Recent research suggests combining glutamine-targeting therapies with dietary energy restriction (DER), which may reduce side effects and enhance therapeutic outcomes (66). Additionally, green tea polyphenols, specifically epigallocatechin gallate (EGCG), have been shown to inhibit glutamate dehydrogenase, a critical enzyme in glutamine metabolism, offering a non-toxic approach to modulating glutamine metabolism in both localised and metastatic cancers, particularly in low-glucose conditions (67).

The breakdown of glutamine is a critical metabolic pathway in cancer cells, providing essential intermediates for the TCA cycle and biosynthesis of nucleotides and amino acids necessary for high rates of protein synthesis and rapid cell division (68). This pathway is particularly vital for cancers with high anabolic growth demands, where glutamine addiction supports tumour growth. Disrupting glutaminolysis through targeted therapies could limit the availability of biosynthetic precursors, thus halting cancer cell proliferation. Glutaminase inhibitors, such as CB-839, specifically target GLS1, the isoform of glutaminase predominantly expressed in cancer cells (68). These inhibitors have shown preclinical efficacy in reducing tumour growth and are being explored in early-phase clinical trials (69). Additionally, tumours with mutations in enzymes like succinate dehydrogenase (SDH) or isocitrate dehydrogenase (IDH), which increase dependency on glutamine metabolism, present opportunities for more targeted therapies to exploit these specific metabolic vulnerabilities, potentially improving treatment outcomes (70).

Targeting Lipid Metabolism and the Tumour Microenvironment for Cancer Therapy

Cancer cells undergo significant reprogramming of lipid metabolism to meet the increased demands for energy, membrane biosynthesis, and signalling molecules required for tumour growth (71). A key process is de novo lipogenesis (DNL), where enzymes like fatty acid synthase (FASN), acetyl-CoA carboxylase (ACC), and ATP-citrate lyase (ACLY) are overexpressed, ensuring a continuous supply of fatty acids for membrane synthesis and energy production. Additionally, cancer cells enhance fatty acid uptake through overexpression of fatty acid transport proteins (FATPs) and CD36, scavenging fatty acids from their environment to support metabolic needs (72). Lipids also act as signalling molecules, influencing crucial pathways like PI3K/Akt signalling and sphingolipid metabolism, which regulate cell proliferation, survival, and metastasis (73). Inhibiting enzymes such as FASN has shown promise in preclinical and clinical studies for selectively targeting cancer cells, with compounds like TVB-2640 and orlistat potentially impairing tumour growth while sparing normal cells (74).

The tumour microenvironment (TME) plays a critical role in modulating lipid metabolism in cancer cells. Cancer-associated fibroblasts (CAFs) and adipocytes contribute fatty acids to tumour cells, particularly under hypoxic conditions, which leads to lipid droplet formation within the cancer cells (75). Tumour-associated macrophages (TAMs), which are metabolically reprogrammed to support tumour growth, also contribute to immune evasion and chemotherapy resistance. These interactions between cancer cells and components of the TME help meet the metabolic demands of the tumour and enhance its ability to survive in a challenging environment (76). Understanding and targeting lipid metabolism in the TME could therefore represent a promising approach for disrupting the metabolic support cancer cells receive from their microenvironment, offering new opportunities for therapeutic intervention (77).

Fatty acid oxidation (FAO), which provides essential energy to cancer cells, especially those resistant to conventional therapies, is another critical pathway that can be targeted for cancer treatment. FAO inhibitors, such as etomoxir, block the transport of long-chain fatty acids into mitochondria, disrupting the energy supply of these cells (78). This approach could enhance the anti-tumour effects of chemotherapy and therapies targeting the androgen receptor, particularly in prostate cancer. However, achieving selectivity for cancer cells and overcoming potential resistance remain challenges. Inhibiting key enzymes involved in lipid metabolism, such as FASN and acyl-CoA synthetase (ACSL), could further disrupt tumour growth and may be explored in combination with other metabolic inhibitors to increase therapeutic efficacy (79). Additionally, targeting the TME itself—by normalising blood supply, altering the extracellular matrix, or modulating immune cells like CAFs and TAMs—holds promise in reducing the metabolic flexibility of cancer cells and improving the effectiveness of metabolic therapies (80).

Epigenetic Regulation of Metabolism in Cancer

Histones, as protein components of chromatin, undergo various post-translational modifications like acetylation, methylation, phosphorylation, and ubiquitination, which influence gene expression by altering chromatin structure. Histone acetylation, facilitated by histone acetyltransferases (HATs), results in an open chromatin structure that enhances the expression of genes involved in glycolysis, while histone deacetylases (HDACs) repress genes related to lipid metabolism (81). Histone methylation, depending on the specific residues and type of methylation, can either activate or repress transcription, regulating enzymes involved in the TCA cycle and nucleotide biosynthesis. Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are also involved in metabolic reprogramming in cancer cells. miRNAs, like miRNA-195, can inhibit enzymes involved in lipid biosynthesis and suppress cancer cell proliferation and metastasis, while lncRNAs influence gene expression and metabolic processes such as amino acid metabolism and redox balance by serving as scaffolds or decoys for chromatin-modifying complexes (82). Metabolic intermediates such as α-ketoglutarate and S-adenosylmethionine (SAM) link metabolism to epigenetic modifications, with α-ketoglutarate acting as a cofactor for DNA and histone demethylases, and SAM and NAD+ playing roles in sirtuin activation and further connecting metabolism to epigenetic regulation (83). This interplay is crucial for cancer progression, and targeting epigenetic modifications has emerged as a promising therapeutic approach in cancer treatment. Epigenetic drugs like DNA methyltransferase inhibitors (e.g., 5-azacytidine) and HDAC inhibitors (e.g., vorinostat) can reactivate silenced metabolic genes and disrupt cancer cell metabolic adaptations (84). DNA methylation, specifically the addition of methyl groups to cytosine residues in CpG dinucleotides, plays a significant role in regulating metabolic pathways in cancer. Hypermethylation of certain genes can

silence important metabolic pathways such as glycolysis, the TCA cycle, and lipid metabolism. For example, the hypermethylation of genes regulating hypoxia-inducible factor (HIF-1α) enhances its stability, promoting the Warburg effect, which drives glycolysis even in the presence of oxygen (85). This metabolic shift supports the high energy and biosynthetic demands of rapidly proliferating cancer cells. Furthermore, methylation can also regulate glutaminolysis, which is crucial for meeting the energy and biosynthetic needs of cancer cells. Metabolic Reprogramming in Cancer: The Role of HIFs, Oncogenes, and Tumor Suppressors (86).

Hypoxia-inducible factors (HIFs) are crucial transcription factors activated under low-oxygen conditions, often seen in tumour environments. These factors drive metabolic reprogramming in cancer cells, inducing a shift from oxidative phosphorylation (OXPHOS) to glycolysis, enabling cells to survive hypoxic conditions. HIF-1α plays a key role in promoting glycolysis by inducing pyruvate dehydrogenase kinase (PDK), which inhibits pyruvate entry into the tricarboxylic acid (TCA) cycle, ensuring energy production despite limited oxygen (87). This shift, known as the Warburg effect, supports continued cancer cell growth and survival. HIF-2α, on the other hand, promotes OXPHOS in specific cancer contexts, such as renal carcinoma with VHL loss, where it enhances mitochondrial function and oxidative metabolism (88). Hypoxia, characteristic of solid tumours due to abnormal vasculature, stabilises HIFs, driving metabolic reprogramming that includes glycolysis, angiogenesis, and epithelial-mesenchymal transition (EMT), all of which contribute to tumor progression and metastasis by helping cancer cells adapt to the oxygen-deprived tumor microenvironment (TME) (89).

In addition to HIFs, oncogenes like MYC and RAS contribute to cancer metabolism by driving anabolic processes that promote the uptake and utilisation of nutrients essential for cancer cell growth (90). MYC stimulates glucose transporter and glycolytic enzyme expression while enhancing glutamine metabolism to support the TCA cycle (91). RAS similarly promotes metabolic pathways to fuel rapid tumour growth (92). Tumour suppressor genes, such as TP53 and LKB1, when lost or mutated, exacerbate these metabolic shifts, particularly by promoting glycolysis and other biosynthetic pathways. Loss of TP53, common in cancer, upregulates glycolysis and contributes to the Warburg effect (93). Similarly, LKB1 loss disrupts cellular regulation, further enhancing the glycolytic phenotype and enabling cancer cells to adapt to altered metabolic demands (94). These genetic alterations, including those involving HIFs, create a highly dependent metabolic environment in cancer cells, allowing them to survive and proliferate in challenging conditions like hypoxia, driving tumour progression.

Role of ROS and OXPHOS in Cancer Metastasis and Stem Cell Therapy Resistance

Reactive oxygen species (ROS) play a crucial role in promoting metastasis by enhancing the expression and activity of matrix metalloproteinases (MMPs), which degrade the extracellular matrix and facilitate cancer cell invasion. ROS also induces epithelial-mesenchymal transition (EMT), a process that grants cancer cells an invasive phenotype, enabling their spread to distant sites and the formation of metastases (95). Additionally, ROS contributes to anoikis resistance, allowing cancer cells to survive in circulation, evade cell death, and establish metastatic colonies in distant organs (96). This combination of effects enhances the metastatic potential of cancer cells, promoting the spread and progression of the disease.

Cancer stem cells (CSCs), a small subpopulation of self-renewing and differentiating tumour cells, are highly dependent on oxidative metabolism (OXPHOS) for survival, particularly under metabolic stress (97). CSCs exhibit metabolic flexibility, enabling them to switch between glycolysis and OXPHOS based on their microenvironment, which allows them to survive in various tumour niches and evade therapies targeting glycolytic cells. Their reliance on OXPHOS is reinforced by enhanced mitochondrial biogenesis and efficient ROS management, making them resilient and difficult to target. This metabolic dependency makes CSCs resistant to conventional therapies targeting glycolysis, and their ability to enter quiescence and undergo EMT adds another layer of resistance (98).

Mitochondrial Protection in Cancer Therapy and Prevention

The hypothesis that impaired mitochondrial energy metabolism underlies many cancers suggests that protecting mitochondria from damage could serve as a preventive strategy. Inflammation, oxidative stress, and mitochondrial dysfunction are key contributors to cancer development (99). Chronic inflammation, often caused by factors like smoking, obesity, and radiation, can lead to mitochondrial damage, triggering neoplastic transformation (100). Preventing inflammation and protecting mitochondria can reduce cancer incidence, with ketone body metabolism playing a protective role by reducing oxidative stress and inflammation

(101). Dietary energy restriction, associated with reduced ROS production and increased mitochondrial efficiency, further protects mitochondrial integrity (102). However, adequate nutrition must be maintained during energy restriction to avoid malnutrition, which could increase cancer risk. Additionally, cancer cachexia, a complication of many cancers, can be mitigated through energy restriction, which limits pro-cachexia molecule production, and omega-3 fatty acids, which support metabolic health and elevate ketone body levels, potentially alleviating cachexia symptoms (103).

Novel Therapeutic Approaches and Personalised Strategies

Understanding cancer as a metabolic disease opens up new therapeutic opportunities that target the altered metabolic pathways cancer cells rely on for growth and survival. Instead of solely focusing on genetic mutations, these approaches aim to restore mitochondrial function or disrupt specific metabolic processes, such as glycolysis and the TCA cycle, to hinder energy production in tumour cells (104). Targeting mitochondrial dysfunction could offer a selective way to eliminate cancer cells while sparing normal cells (105). Combination therapies, such as pairing glycolysis inhibitors with conventional treatments like chemotherapy and immunotherapy, have the potential to improve therapeutic efficacy by targeting multiple aspects of cancer cell metabolism (106). Additionally, glycolytic inhibitors, which disrupt cancer cell metabolism by blocking key enzymes in glycolysis and glucose transport, offer promising new avenues for cancer therapy, particularly in tumours that rely heavily on aerobic glycolysis (107).

Metabolic inhibitors, such as lactate dehydrogenase (LDH) inhibitors, are also being explored for their potential to induce oxidative stress, reduce tumour acidification, and enhance anti-tumour responses (108). These inhibitors can work synergistically with other therapies, like immune checkpoint inhibitors, to reduce metastasis and improve treatment outcomes (109). Similarly, dietary energy restriction, which limits the availability of key nutrients such as glucose and glutamine, has shown promise in reducing tumour growth across multiple cancer types (110). Personalised treatment approaches based on an individual's genetic and metabolic profile are gaining traction, with adaptive therapies being developed to adjust treatment according to tumour responses and resistance mechanisms. This personalised approach, combined with optimised combination therapies, could help overcome resistance and minimise side effects, providing more effective and tailored treatments for cancer patients.

Challenges and Opportunities in Targeting Cancer Metabolism for Therapeutic Development

Targeting cancer metabolism presents numerous challenges due to the metabolic plasticity and adaptability of cancer cells. These cells can adjust to environmental stresses such as nutrient deprivation, hypoxia, and fluctuating blood supply, utilising different nutrient sources or switching metabolic pathways to sustain growth. This metabolic flexibility and plasticity enable cancer cells to bypass metabolic inhibitors by relying on alternative pathways or depending on neighbouring stromal cells for nutrients (111). Moreover, tumour heterogeneity complicates the development of universal metabolic inhibitors, as different cancer cells within the same tumour may rely on distinct metabolic processes, making it difficult to target all tumour cells effectively (112). The tumour microenvironment (TME) further influences these metabolic shifts, adding another layer of complexity to therapy development (11). Additionally, as cancer cells evolve, they often develop resistance mechanisms through genetic mutations and epigenetic changes, reducing the long-term efficacy of metabolic inhibitors.

Despite these challenges, cancer metabolism remains a promising area for therapeutic development. Understanding the mechanisms behind cancer cells' altered metabolic pathways can lead to innovative therapies aimed at targeting these vulnerabilities, offering a potential shift from conventional therapies. However, the heterogeneity of tumours, the influence of the TME, and the ability of cancer cells to adapt to metabolic therapies highlight the need for combination strategies. Integrating metabolic inhibitors with other treatments, such as immunotherapies and chemotherapies, may enhance their effectiveness and help overcome resistance, leading to more durable and targeted cancer treatments (114).

Conclusion

The increasing body of research underscores cancer as primarily a disease of energy metabolism, offering new insights into tumour growth, survival, and metastasis. Central to this understanding is mitochondrial dysfunction, which triggers significant metabolic changes in cancer cells, shifting energy production from oxidative phosphorylation to substrate-level phosphorylation. Key processes such as the Warburg effect, oxidative phosphorylation, glutaminolysis, and lipid metabolism contribute to the rapid proliferation and survival of cancer cells, enabling them to thrive despite impaired

mitochondrial function (115). These metabolic shifts highlight potential therapeutic targets that could disrupt the energy pathways driving cancer progression.

While the complexity and heterogeneity of cancer metabolism pose challenges, targeting specific metabolic processes, such as glycolysis, oxidative phosphorylation, and glutaminolysis, shows significant therapeutic promise. Inhibitors like glycolysis blockers, oxidative phosphorylation inhibitors, and glutaminolysis inhibitors (e.g., CB-839) offer potential treatment avenues. Additionally, targeting critical signalling pathways like mTOR and PI3K/AKT may enhance therapeutic efficacy (116). However, due to the metabolic plasticity of cancer cells, combination therapies will likely be needed to overcome resistance and maximise treatment effectiveness (117). The development of reliable biomarkers for metabolic targeting will also be key for personalised treatment, allowing better patient selection and monitoring. Integrating metabolic inhibitors with conventional treatments such as chemotherapy and immunotherapy could transform cancer care, improving outcomes and leading to more effective, personalised therapies. Ongoing research into cancer metabolism and its regulation within the tumour microenvironment is essential for creating novel, sustainable treatment strategies for cancer prevention and management.

List of Abbreviations

ACSL - Acyl-CoA Synthetase Long Chain Family Member; Akt - Protein Kinase B (also known as AKT Serine/Threonine Kinase); AML - Acute Myeloid Leukemia; AMPK - AMP-activated Protein Kinase; CAFs - Cancer-Associated Fibroblasts; CSCs - Cancer Stem Cells; EMT - Epithelial-Mesenchymal Transition; FAO - Fatty Acid Oxidation; FASN - Fatty Acid Synthase; FH – Fumarase ; GAPDH - Glyceraldehyde-3-Phosphate Dehydrogenase; GLUT1 - Glucose Transporter Type 1; HATs - Histone Acetyltransferases; HDACs - Histone Deacetylases; HIF-1α - Hypoxia-Inducible Factor 1 Alpha; HIFs - Hypoxia-Inducible Factors; HK2 - Hexokinase 2; IDH - Isocitrate Dehydrogenase;LDH - Lactate Dehydrogenase;LDHA - Lactate Dehydrogenase A; lncRNA - Long Non-Coding RNA; miRNA – MicroRNA; MMPs - Matrix Metalloproteinases; mTOR - Mechanistic Target of Rapamycin; MYC - Myelocytomatosis Proto-Oncogene ; OXPHOS - Oxidative Phosphorylation; p53 - Tumor Protein 53; PGC-1α - Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha; PI3K - Phosphoinositide 3-Kinase; PI3K/AKT - Phosphoinositide 3-Kinase/Protein Kinase B; PKM2 - Pyruvate Kinase M2; Ras - A family of oncogenes involved in cell signaling; RAS - Rat Sarcoma Virus (Ras family of oncogenes); ROS - Reactive Oxygen Species;SAM - S-Adenosylmethionine; SDH - Succinate Dehydrogenase; TAMs - Tumor-Associated Macrophages; TCA cycle - Tricarboxylic Acid Cycle (also known as the Citric Acid Cycle or Krebs Cycle); TIGAR - TP53-Induced Glycolysis and Apoptosis Regulator; TME - Tumor Microenvironment;TP53 - Tumor Protein 53 (a tumor suppressor gene); VEGF - Vascular Endothelial Growth Factor; 2-HG - 2-Hydroxyglutarate

Declarations

Ethics approval and consent to participate

This study does not involve human or animal subjects and therefore does not require ethics approval. All data used in this study are publicly available.

Consent for publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials

Data supporting this study's conclusions are available from publicly accessible databases (PubMed, Google Scholar, Web of Science, Scopus, Embase, and clinicaltrials.gov) and can be provided upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

UEA conceptualised, designed, and drafted the manuscript. IOJ contributed to data analysis, literature review, and writing. EO reviewed and interpreted metabolic pathways. ANY contributed to therapeutic strategies and data extraction. DLT assisted with the methodology review and manuscript drafting. All authors revised the manuscript, approved the final version, and are accountable for the work.

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