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DERLEME REVIEW

Metabolic Reprogramming in Early Cancer: Altered Glucose and Its Role in Tumorigenesis

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Abstract

Metabolic reprogramming is a hallmark of cancer, playing an essential role in carcinogenesis and the initial steps of cancer development. This phenomenon involves alterations in cellular metabolism, particularly in using sugars, which provide the essential energy and building blocks for tumour growth and propagation. This review focuses on the metabolic reprogramming associated with early cancer and its impact on sugar metabolism. Cancer cells exhibit enhanced glucose uptake and utilisation, commonly known as the Warburg effect, which allows for rapid Adenosine Triphosphate production and biomass synthesis. Additionally, cancer cells demonstrate increased glycolytic flux, diverting glucose metabolites towards anabolic pathways that support cell growth. Oncogenic signalling pathways, including the activation of key regulators and alterations in tumour suppressor genes such as the p53 gene, drive these alterations in sugar metabolism. Renewing sugar metabolism in cancer cells provides a selective advantage, facilitating tumour survival and progression. Moreover, metabolic alterations in early cancer promote the generation of intermediates for biosynthesis, redox balance, and post-translational modifications, further contributing to tumorigenesis. Understanding the complexities of metabolic reprogramming in early cancer is crucial for developing effective treatment strategies that target metabolic vulnerabilities. Therapeutic interventions aimed at disrupting cancer cells' addiction to altered sugar metabolism hold great promise in halting tumour growth and improving patient outcomes.

Keywords: *Glycolysis, Cancer cells, PPP, GLUTs, NADPH*

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INTRODUCTION

Metabolic reprogramming is increasingly recognised as a fundamental characteristic of cancer, playing a vital part in tumour initiation, development, and metastasis. This process involves systematic alterations in the metabolic ways of cancer cells, allowing them to adjust to their microenvironment and meet the heightened demands for energy and biosynthetic precursors essential for rapid propagation. Otto Warburg first described the phenomenon, noting that cancer cells mainly utilise glycolysis for energy production, even in the absence of oxygen, a phenomenon called the Warburg effect (Figure 1) (1, 2).

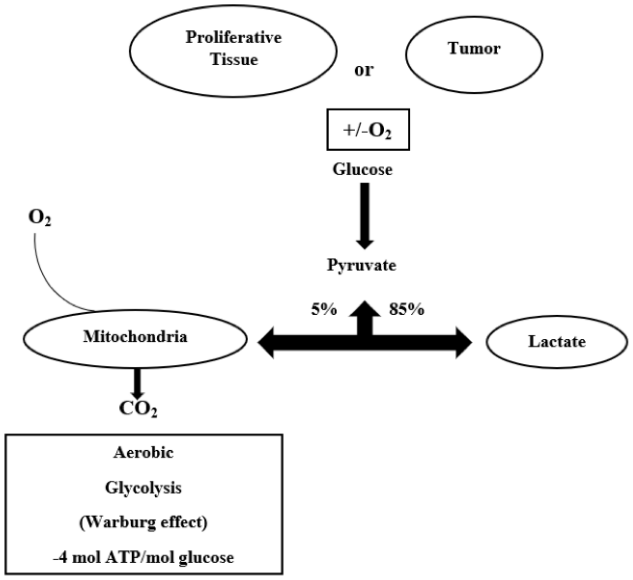

Figure 1. An overview of the Otto Warburg effect. This effect has been documented for over 90 years. During the 1920s, Otto Warburg and his associates observed that tumours absorbed significantly more glucose than the adjacent tissue. The glucose metabolism, intensively investigated, was designated the Warburg Effect in the early 1970s, which is essential for tumour growth. In tumours and other proliferative or growing cells, the glucose absorption rate significantly increases, producing lactate, even in the presence of oxygen and fully functional mitochondria. To eradicate tumour cells, they must be deprived of energy, glucose, and oxygen.

Altered glucose metabolism is critical to cancer biology, significantly influencing tumour growth and progression. Otto Warburg's definition of aerobic glycolysis in the 1920s highlights how cancer cells preferentially use glycolysis to produce energy, even without oxygen. This metabolic reprogramming enables cancer cells to satisfy their heightened bioenergetic and biosynthetic requirements, promoting fast growth and survival in adverse conditions (3).

In early cancer development, alterations in glucose metabolism are often driven by genetic mutations that affect key regulatory pathways. Oncogenes and tumour suppressor genes play pivotal roles in this metabolic shift, leading to enhanced glucose uptake and altered enzymatic activities favouring glycolysis and complete oxidative phosphorylation. The upregulation of glucose transporters (GLUTs) is a common adaptation that enables cancer cells to maximise glucose influx, thereby supporting their aggressive growth patterns. Furthermore, lactate accumulation as a byproduct of glycolysis contributes to an acidic tumour microenvironment, promoting invasion and metastasis (4, 5).

Understanding these metabolic alterations provides valuable insights into cancer biology and unlocks new avenues for therapeutic intervention. Targeting the unique metabolic pathways that cancer cells exploit could enhance treatment effectiveness and overcome resistance to conventional therapies. This review focuses on the metabolic reprogramming associated with early cancer and its impact on sugar metabolism.

Altered Glucose Metabolism in Early Cancer

Cancer cells exhibit a modified metabolism, characterised by increased glucose uptake and enhanced glycolysis. This metabolic transformation is a characteristic of cancer cells. Aerobic glycolysis is the most significant acknowledged metabolic irregularity in cancer cells, characterised by elevated glucose consumption and lactate synthesis despite the availability of oxygen and operational mitochondria (6, 7).

Cancer metabolism exhibits significant heterogeneity, reflecting different cancers' genetic, epigenetic, and environmental contexts. For instance, whereas the Warburg effect is characterised by aerobic glycolysis, prevalent in several malignancies, some tumours may primarily utilise glutaminolysis or fatty acid oxidation to fulfil their bioenergetic and biosynthetic requirements. This metabolic variety can manifest within the same tumour, where various areas may have differing metabolic profiles based on dietary availability and oxygenation levels (8). This intricacy hinders the development of treatments, as therapies targeting one route may be unsuccessful against others. Resolving this issue necessitates stratifying tumours according to their metabolic characteristics and customising therapies appropriately. Progress in metabolomics and imaging technologies may significantly contribute to identifying and classifying metabolic abnormalities, facilitating precision oncology (9).

Increased Glucose Uptake and Utilisation

Cancer cells exhibit a fast increase in glucose absorption and ferment it straight into lactate. In the 1920s, Nobel Prize winner Otto Warburg initially identified the modified glucose metabolism. The earliest identified metabolic anomaly linked to cancer was glucose intolerance. Cancer cells have unique modifications in their metabolic pathways, including heightened glucose absorption, accelerated glutaminolysis, and modified lipid metabolism (10).

Transformed cells exhibit an increased glucose uptake rate that exceeds the requirement for ATP production. Glucose facilitates biomass production and modulates cellular signalling, which is essential for oncogenic advancement. The transmission of glucose across the plasma membrane is a critical rate-limiting step in glucose utilisation. Metabolic adaptations are intricately linked to changes in cellular behaviour. In the last twenty years, there has been an increasing focus on cancer breakdown, especially on glucose breakdown (11). Cancer cells can alter energy breakdown to counteract the increased biogenic stresses essential to growth and uncontrolled development. Normal tissue cells predominantly generate ATP via mitochondrial oxidative phosphorylation. In these types of cells, glucose is converted to pyruvate by glycolysis, with the bulk of pyruvate entering mitochondrial oxidative breakdown for sustainable energy production (12, 13).

GLUT transporters use preexisting sugar concentration gradients across the plasma membrane to enable translocation. SGLT proteins facilitate glucose uptake into cells against the concentration gradient, necessitating considerable energy expenditure. Sugars are predominantly derived from food following the hydrolysis of disaccharides and polysaccharides. However, synthesis may also occur in organs such as the liver. Nutritional sweeteners are absorbed by enterocytes that line the lumen of the small intestine. Furthermore, dietary and synthesised glucose must be transmitted throughout the organism's bloodstream. Glucose transfer occurs via glucose transporter proteins located in the plasma membranes of cells. The localisation of glucose transporters is intracellularly controlled by divergence, particularly in enterocytes, where each cellular lateral displays unique transporters with differing attributes (14).

Carbohydrate breakdown occurs in the small intestine, while monosaccharides are absorbed into the bloodstream. Three hormones control blood glucose levels: glucagon, epinephrine, and insulin. Increased glucose absorption prompts the pancreas to produce insulin. Insulin facilitates the transport of glucose into hepatic and muscular cells, where the majority of glucose is converted into glycogen through a process known as glycogenesis. Cancer cell proliferation is characterised by an increased need for glucose to support aerobic glycolysis, hence facilitating the production of cellular metabolites essential for biomass generation and nutritional signalling (15).

Otto Warburg's early 1900s paper suggested a potential involvement of glucose metabolism in cancer growth. Recent in vivo studies indicate that short-term starvation and glucose limitation during chemotherapy can enhance tumour suppression, augment chemotherapy efficacy, and prolong cancer-free lifespans in murine models of melanoma, breast cancer, and neuroblastoma by reducing toxicity in healthy tissues. This highlights the advantages of targeting glucose metabolism for cancer treatment (16). Neoplastic cells have long been recognised for reconfiguring their energy metabolism to satisfy elevated bioenergetic requirements that facilitate fast and unregulated proliferation. Normal, differentiated cells predominantly utilise oxidative phosphorylation of mitochondria to produce the energy and biomass required for cellular processes; conversely, many cancer cells possess substantial modifications in their metabolic pathways and rely on aerobic glycolysis, a process referred to as aerobic glycolysis (17).

Enhanced Glycolysis and Lactate Production
Cancer cells have increased glycolysis and lactate synthesis, a characteristic of aerobic glycolysis. Ninety-three years ago. This altered energy metabolism pathway is characterised by improved aerobic glycolysis and unnecessary lactate formation. Cancer cells in hypoxic environments consume high glucose levels and secrete high lactic acid levels from the cytoplasm. Lactate is predominantly generated by cancer glycolysis and is not only a waste product; it is released into the tumour microenvironment (TME) and seen as a substantial immune suppressor by tumours(18). The prevalent inclination of malignancies towards lactic acid-producing metabolic pathways has suggested that their altered metabolism provides growth benefits, including reduced vulnerability to hypoxic stress. Recent data, however, indicate that it may lead to a new method of cancer survival. There is growing evidence that tumours might evade immune obliteration by constraining the anticancer immune response via maintaining a comparatively low pH in their microenvironment (19).

Glycolysis is the catabolic pathway through which glucose undergoes its first change to yield energy. In typical cells, glucose undergoes additional metabolism via the tricarboxylic acid cycle and mitochondrial oxidative phosphorylation after glycolysis. Cancer cells have a heightened glucose intake (20). Glycogen exists in the liver and muscles. The process of converting glycogen into glucose is known as glycogenolysis. Metabolic compounds produced by glycolysis interact with proteins, nucleic acids, and lipids. Glucose is the pivotal molecule in carbohydrate catabolism and anabolism. Several key routes of the breakdown of carbohydrates are connected to the transformations of glucose, as glucose is the primary sugar in the bloodstream and the body's energy source (Figure 2.2) (10).

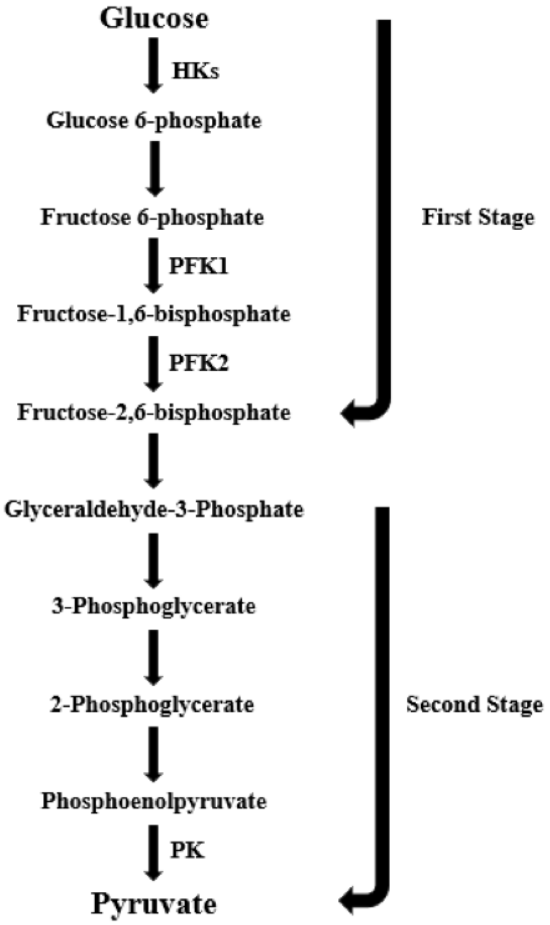

Figure 2.2. Glycolysis. Glycolysis has two phases: the initial phase utilises ATP, while the subsequent phase produces ATP. Three essential responses occur in cancer cells. First, HK facilitates the transformation of glucose into glucose-6-phosphate. Second, Fructose-6-phosphate is transformed into fructose 1,6-bisphosphate by PFK1 and fructose 1,6-bisphosphate is then turned into fructose 2,6-bisphosphate by PFK2. Third, phosphoenolpyruvate is converted into pyruvate-by-pyruvate kinase. Bent missiles denote HK, PFK1, and PK overexpression in cancer cells. HK refers to hexokinase; PK denotes pyruvate kinase; PFK signifies phosphofructokinase (19).

Glycolysis is a ubiquitous mechanism for glucose breakdown in plants and animals. It is present in every cell of the human body. The glycolytic process converts one glucose molecule into two pyruvic acid molecules, with the released energy being stored as ATP and the reducing equivalent of NADH. The principal function of glycolysis is to supply energy and intermediates for subsequent metabolic pathways. The primary bases of glucose for glycolysis are nutritional carbohydrates and cellular glycogen (22). During the early stages of carcinogenesis, unregulated cell growth causes cancer cells to dislodge from blood vessels, depriving them of oxygen and essential nutrients. Glucose and oxygen can only reach the core cells of a non-vascularized tumour by diffusing through the cell membrane and the peripheral coatings of tumour cells. Nonetheless, incomplete oxygen pressure decreases to significantly low levels of hundreds of mm from blood vessels**.** Since the 1920s, it has been demonstrated that cancer cells exhibit a considerably elevated glucose uptake via a glycolytic pathway that does not direct pyruvate to the Krebs cycle but instead

converts pyruvate to lactate, the purported aerobic glycolysis (23).

Cancer cells primarily obtain energy from glucose through glycolysis, producing lactic acid, even in highly aerobic environments, a phenomenon initially identified by Otto Warburg. This effect is another name for aerobic glycolysis, which is significantly less energy-efficient compared to the oxidative phosphorylation route (24). Cancer cells also obtain energy via enhanced non-glucose-dependent mechanisms, including increased glutaminolysis in aerobic environments. Aerobic glycolysis and enhanced glutaminolysis are combined and termed reprogrammed energy metabolism,' a condition well recognised as a fundamental metabolic characteristic of cancer. Numerous studies have hypothesised about the benefits of aerobic glycolysis in cancer, although the causal link between this metabolic alteration and cancer progression remains ambiguous. Recent investigations suggest that modified energy metabolism may facilitate cancer development by aiding tumour escape from immune destruction (25).

Cancer cells must also contend with oxidative stress and immune surveillance, which can alter their metabolic pathways. Lactate from glycolysis acidifies the tumour microenvironment, inhibiting immune cell activity and facilitating cancer invasion (26). Lactate production from glycolysis acidifies the tumour microenvironment (TME), inhibiting immune cell function and facilitating tumour invasion. These external factors underscore the necessity for a comprehensive approach to cancer metabolism, considering the interaction between cancer cells and their microenvironment. Understanding these dynamics may inform the development of combination therapies that disrupt the metabolic interactions within the TME (5).

Activation of the Pentose Phosphate Pathway

The pentose phosphate pathway (PPP) enhances glucose metabolic diversion in neoplastic cells. It is crucial for the sustenance and propagation of cancer cells, as it produces pentose phosphate for nucleic acid synthesis and creates NADPH, which is essential for reductive metabolism and mitigating oxidative stress in tumour cells. The PPP is crucial for nucleotide synthesis in rapidly proliferating cells. Recent studies indicate that it is essential in modulating cancer cell proliferation by providing ribose-5-phosphate to the cells. The PPP comprises non-oxidative and oxidative phases (26).

The PPP, which diverges from glycolysis at the early phase of glucose metabolism, is crucial for ribonucleotide synthesis and is a principal source of NADPH. The NADPH is essential for fatty acid synthesis and neutralising reactive oxygen species (ROS). Consequently, the PPP enables glycolytic cancer cells to fulfil their anabolic requirements and mitigate oxidative damage**.** Over the past few years, there has been a substantial increase in investigations into cancer metabolism. The PPP is a significant mechanism for the breakdown of glucose, channelling glucose into its oxidative pathway, which yields a reduced form of nucleic acids and NADPH. The PPP is essential in controlling cancer cell proliferation and encompasses several enzymes**.** Hepatocellular carcinoma (HCC) ranks among the most prevalent malignancies globally**.** Breast cancer ranks as the second most prevalent cancer globally, with nearly two million new cases diagnosed each year (27, 28). Lung cancer is the primary reason for cancer-related death globally. A significant characteristic of these three cancers is a change in the breakdown of glucose. A more profound sympathy for this metabolic change may thus improve plans for the prevention, initial diagnosis, and treatment of hepatocellular carcinoma, lung cancer, and breast cancer (29).

Cancer cells have an elevated need for glucose. Consequently, pinpointing the precise elements of glucose metabolism implicated in cancer's aetiology may reveal innovative treatment targets. There has been a renewed focus on the role of the pentose phosphate pathway in cancer. This metabolic route benefits rapidly proliferating cells by supplying nucleotide precursors and facilitating the regeneration of the reducing agent NADPH, which aids in scavenging reactive oxygen species (ROS) (30).

Cancer cells primarily use glycolysis to produce energy from glucose. In the 1920s, German biologist Otto Warburg discovered that cancer cells metabolise significant quantities of glucose and convert it to lactate, even in oxygen-rich environments, a phenomenon known as aerobic glycolysis or the Warburg effect. Glucose undergoes glycolysis, is transformed into 3-carbon lactate, and is expelled from cells rather than further oxidised. In cancer cells, the metabolism of a single glucose molecule produces just two to four ATP molecules, unlike in normal cells (26). Recent research indicates that metabolic reprogramming is a crucial phase in carcinogenesis. Several oncogenes and tumour suppressors regulate metabolism, and metabolic alterations are essential to transitioning from normal to malignant development (31).

The PPP has two stages: the non-oxidative and the oxidative phase. The key regulatory enzyme in the pentose phosphate system is glucose-6-phosphate dehydrogenase (G6PD). G6PD catalyses the oxidation of glucose-6-phosphate to 6-phosphoglucono-δ-lactone, yielding NADPH as a by-product. G6PD is overexpressed in several malignancies, is negatively controlled by the tumour suppressor p53, and is negatively regulated by the tumour suppressor p53 (32). G6PD was recommended as a biomarker for prostate cancer more than thirty years ago (Figure 2.3) (30).

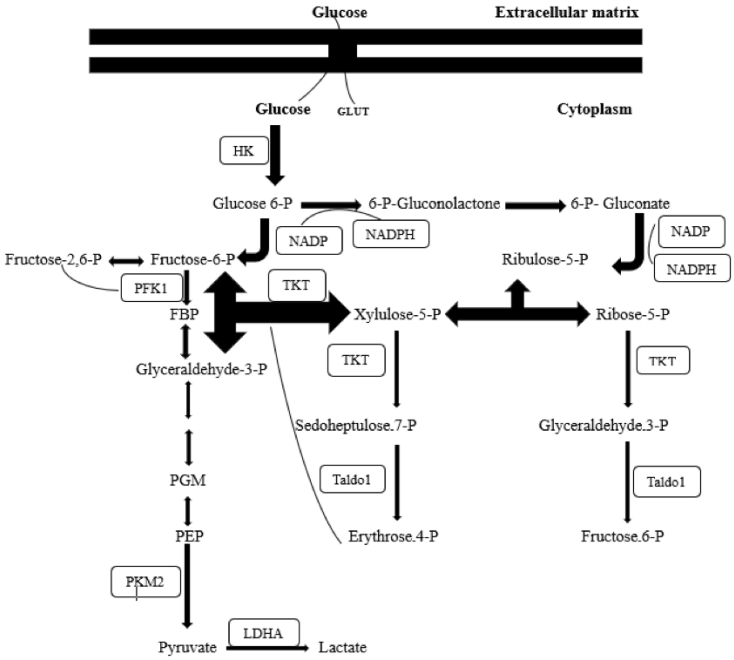

Figure 2.3. A schematic illustration of the PPP and glycolysis is presented. The oxidative branch of the pentose phosphate pathway produces NADPH, which is utilised in biosynthetic pathways for nucleotides, lipids, and antioxidant defence. The reversible non-oxidative pathway generates ribose-5-phosphate from the oxidative pathway and glycolytic intermediates. Solid black lines denote glycolytic flow; green arrows indicate the oxidative branch of the pentose phosphate pathway (PPP), and light blue arrows show the multi-step processes of the non-oxidative branch of the PPP. To provide clarity, each element of the metabolic process has been shortened. PPP refers to the pentose phosphate pathway; G6PD denotes glucose-6-phosphate dehydrogenase; 6PGD signifies 6-phosphogluconate dehydrogenase; TKT represents transketolase; Taldo1 indicates transaldolase; HK stands for hexokinase; GLUT pertains to glucose transporters; PFK1 is phosphofructokinase-1; PGM refers to phosphoglycerate mutase; PKM2 denotes pyruvate kinase (PK)-M2; LDHA signifies lactate dehydrogenase A; FBP indicates fructose-1,6-bisphosphate; PEP refers to phosphoenolpyruvate (26).

Alterations in Glucose Transporters and Regulatory Enzymes

Glucose transporters and regulatory enzymes are frequently altered in early-stage cancer. Malignant cells exhibit heightened breakdown, increased glucose demands, and enhanced glucose absorption. Glucose transport across the plasma membrane in mammalian cells is the key rate-limiting step in glucose breakdown, facilitated by glucose transporter (GLUT) proteins. Glucose permeates cells through 12 functioning (GLUTs), labelled GLUT-1 to GLUT-12. The mainstream is tissue-specific, including GLTU-1 (found in all tissues but primarily in the brain and erythrocytes), GLUT-2 (found in the liver), GLUT-3 (found in the brain), GLUT-4 (found in muscle and adipose tissue), and GLUT-5 (found in the small intestine). GLUTs are essential membrane proteins characterised by twelve transmembrane spirals, with both the amino and carboxyl termini directed towards the cytoplasmic side of the plasma membrane (33). GLUT proteins convey glucose and other hexoses through a facilitated diffusion mechanism, which posits that the transporter presents a single substrate binding site to the extracellular or intracellular environment (34). Brown et al. observed the expression of GLUT-1, 2, 3, 4, and 5 in paraffin-embedded specimens from 12 primary human breast tumours and 8 lymph node metastases from 2 patients. GLUT-1 was detected in all original breast carcinomas and lymph node metastases, with expression observed on the cell membrane and within the cytoplasm of tumour cells. However, there was considerable heterogeneity (both intra- and inter-tumoral) in the percentage of constructive cells and the strength of discoloration (35).

Therapeutic Implications

Targeting metabolic pathways in cancer frequently encounters adaptive resistance. Tumours exhibit significant metabolic plasticity, transitioning to alternative pathways when their primary energy sources are compromised. For instance, when glycolysis is inhibited, certain cancer cells augment their dependence on oxidative phosphorylation or fatty acid oxidation to maintain growth (36, 37). Resistance to pentose phosphate pathway (PPP) inhibitors may similarly occur via the activation of compensatory metabolic pathways. This adaptive capacity highlights the necessity of recognising and concurrently addressing various metabolic weaknesses. Integrating metabolic inhibitors with standard treatments, such as chemotherapy or immunotherapy, may decrease the likelihood of resistance. Moreover, longitudinal investigations monitoring metabolic alterations during therapy may elucidate resistance mechanisms and guide adaptive therapeutic approaches (26, 38).

Potential metabolic targets, including glycolytic enzymes and glucose transporters, are crucial for basic cellular functions, raising concerns about off-target effects and systemic toxicity. Glucose transporter 1 (GLUT-1), a prevalent target in cancer metabolism, is widely expressed in organs such as the brain and red blood cells, rendering its blockage perilous. Addressing this difficulty requires the creation of delivery mechanisms specifically targeting cancer cells, such as nanoparticle-based drug carriers or antibody-drug conjugates. Another strategy involves identifying cancer-specific isoforms or alterations of metabolic enzymes that are not present in normal cells. Progress in structural biology and computer modelling may facilitate the creation of highly selective inhibitors, reducing collateral harm while successfully targeting cancer metabolism (39). Metabolic reprogramming in neoplastic cells is closely associated with immune evasion. Lactate buildup in the tumour microenvironment inhibits the function of cytotoxic T cells and natural killer cells, facilitating cancer survival. Cancer cells often outcompete immune cells for essential resources, such as glucose and amino acids, weakening the immune response. Focusing on these metabolic connections offers a viable strategy for improving immunotherapy. Integrating checkpoint inhibitors with drugs that modify the cancer microenvironment, such as lactate dehydrogenase or glucose metabolism inhibitors, may enhance anti-tumour immune responses. Investigating the bidirectional link between cancer metabolism and immune cell activity is vital for devising synergistic treatment methods (40).

CONCLUSION

Metabolic reprogramming, namely the preferential use of glucose via aerobic glycolysis, termed the Warburg effect, constitutes a fundamental characteristic of early carcinogenesis. This metabolic change is a consequence of malignancy and a basic catalyst supporting cellular transformation, proliferation, and survival in adverse microenvironments. Our review elucidates that cancer cells, especially in the first stages, demonstrate a significant alteration in glucose metabolism, marked by increased glucose transporters, augmented glycolytic flux, and redirection into anabolic pathways, including the pentose phosphate pathway (PPP). These modifications facilitate bioenergetic requirements, maintain redox equilibrium, and enable macromolecular production crucial for fast proliferation.

Recent findings reveal that metabolic adaptability provides cancer cells a substantial survival advantage, enabling them to circumvent immune monitoring and prosper in hypoxic conditions. Lactate, hitherto regarded solely as a metabolic byproduct, is now a pivotal agent in immune evasion and microenvironmental alteration. The activation of the PPP, facilitated by enzymes such as G6PD and governed by critical oncogenes and tumour suppressors, including p53, underscores the dual function of glucose metabolism in promoting nucleotide manufacture and antioxidant defence.

Targeting glucose metabolism presents significant therapeutic potential; yet, cancer cells' intrinsic flexibility requires a multi-targeted strategy. Future techniques should surpass monotherapies by using metabolic inhibitors alongside immunotherapies, chemotherapy, or radiation to prevent adaptive resistance. This highlights the necessity for dynamic and longitudinal metabolic monitoring of tumours to discern context-specific vulnerabilities.

Authors' contributions

The authors contributed equally. Conceptualization: A.S., A.M.Q..; Software and Resources: A.M.Q., A.H.H.; Figures: A.M.Q.; Literature Review; A.M.Q., A.H.H.; Revision and Supervision: A.M.Q., A.S.; Manuscript Preparing: A.H.H., A.M.Q. The authors have reviewed and consented to the published version of the manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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