

# THE WARBURG EFFECT AND HISTOLOGICAL FEATURES OF CANCER CELLS: A NARRATIVE REVIEW

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## Abstract

**Background:** Cancer cells frequently alter glucose metabolism and convert a large proportion of glucose to lactate even when oxygen is available. This phenomenon, known as the Warburg effect or aerobic glycolysis, is one of the best-known examples of metabolic reprogramming in malignant cells. At the same time, cancer is diagnosed microscopically by changes in cell and tissue morphology, including nuclear atypia, loss of differentiation, increased mitotic activity, necrosis, abnormal vascular patterns and invasive growth.

**Objective:** This narrative review summarizes the Warburg effect and discusses how altered tumor metabolism may contribute to, or coexist with, common histological features of malignancy.

**Methods:** A narrative literature search was performed primarily using PubMed and the reference lists of relevant reviews. English-language articles concerning aerobic glycolysis, cancer metabolism, hypoxia, lactate, tumor morphology, necrosis, angiogenesis and histological markers were considered. Classic papers were included where necessary to explain the development of the Warburg concept.

**Results:** Aerobic glycolysis is promoted by oncogenic signaling and hypoxia-related pathways involving PI3K/AKT/mTOR, MYC, HIF-1, glucose transporters and glycolytic enzymes. This metabolic program provides biosynthetic intermediates and redox support for rapidly proliferating cells and produces lactate that modifies the tumor microenvironment. Histologically, highly proliferative tumors may show increased mitoses, high nuclear-to-cytoplasmic ratios and reduced differentiation, while rapidly enlarging solid tumors often develop hypoxic areas, necrosis and irregular neoangiogenesis. However, these microscopic features are not caused by glycolysis alone and reflect the combined effects of genomic instability, altered differentiation, microenvironmental stress and tumor-stromal interactions.

**Conclusion:** The Warburg effect is best understood as one component of a broader metabolic phenotype that supports malignant growth. Linking metabolism with histology provides a useful framework for understanding why aggressive tumors often display characteristic microscopic patterns, while also emphasizing the biological heterogeneity of cancer.

**Keywords:** Warburg effect; aerobic glycolysis; cancer metabolism; histology; tumor hypoxia; lactate; necrosis; angiogenesis.





## Introduction

Cancer is not defined by one molecular abnormality or one microscopic appearance. It develops through the accumulation of genetic, epigenetic and environmental changes that allow cells to proliferate, survive, invade surrounding tissues and interact with the host in abnormal ways. Modern cancer biology therefore considers malignant transformation as a combination of altered signaling, disrupted differentiation, genomic instability, immune escape and metabolic reprogramming. Reprogramming of cellular metabolism is now accepted as a core hallmark of cancer [1,2].

One of the earliest observations in cancer metabolism was made by Otto Warburg, who noted that tumor cells consume large quantities of glucose and produce lactate even when oxygen is present [3]. This behavior differs from the simplified textbook model in which normal cells use glycolysis mainly under oxygen-limited conditions and rely more strongly on mitochondrial oxidative phosphorylation when oxygen is available. The cancer-associated preference for high glycolytic flux in the presence of oxygen became known as the Warburg effect, or aerobic glycolysis [4,5].

The Warburg effect does not mean that cancer-cell mitochondria are always defective or inactive. Many tumors retain functional oxidative phosphorylation and can shift between glucose, glutamine, fatty acids and lactate according to nutrient availability [2,6]. Aerobic glycolysis is therefore better viewed as part of a flexible metabolic program. Its advantages include rapid generation of metabolic intermediates for nucleotide, amino-acid and lipid synthesis, maintenance of redox balance, support of cell proliferation and production of lactate that can influence the surrounding tumor microenvironment [4-7].

Histopathology examines the structural consequences of malignant transformation. Common microscopic features of cancer include increased nuclear size, a high nuclear-to-cytoplasmic ratio, nuclear pleomorphism, hyperchromasia, prominent nucleoli, loss of normal tissue organization, reduced differentiation and increased or abnormal mitotic figures. In solid tumors, areas of hypoxia, necrosis, stromal reaction and disorganized blood vessels may also be observed. These features are familiar to medical students and pathologists, but the biological processes underlying them are complex and not always directly visible on routine hematoxylin and eosin staining [8].

The relationship between metabolism and morphology is therefore attractive but must be described carefully. Aerobic glycolysis does not independently create every histological feature of cancer. Instead, metabolic reprogramming works together with oncogenic signaling, genome instability, altered cell-cycle control, hypoxia and changes in the microenvironment. The purpose of this review is to summarize the Warburg effect and discuss how it relates to major cellular and tissue-level histological features of malignancy.

## 2. Methods

This article was prepared as a narrative review. Literature was searched primarily through PubMed using combinations of the terms "Warburg effect," "aerobic glycolysis," "cancer metabolism," "tumor histology," "nuclear morphology," "tumor hypoxia," "lactate," "GLUT1," "necrosis," "angiogenesis," "dedifferentiation" and "tumor microenvironment." Reference lists of major reviews were also examined to identify relevant original and classic publications.

Priority was given to peer-reviewed English-language reviews, mechanistic studies and pathology-oriented articles that could connect metabolic changes with recognizable tumor morphology. Most





sources were published after 2000, while historically important earlier work was retained when necessary. Because this was a narrative rather than a systematic review, no formal meta-analysis, risk-of-bias scoring or PRISMA selection process was performed. Evidence was synthesized under two broad themes: mechanisms of aerobic glycolysis and histological changes that may be supported or modified by the resulting metabolic state.

### 3. Results

#### 3.1. The basic metabolic pattern of the Warburg effect

Glucose entering the cell is converted through glycolysis to pyruvate. In many differentiated cells under aerobic conditions, pyruvate enters mitochondria and is oxidized through the tricarboxylic acid cycle and oxidative phosphorylation. In cells showing the Warburg phenotype, a larger proportion of pyruvate is converted to lactate by lactate dehydrogenase despite the presence of oxygen [4,5]. The ATP yield per glucose molecule is lower than that of oxidative phosphorylation, but glycolysis can proceed rapidly when glucose is abundant.

The apparent inefficiency of aerobic glycolysis becomes more understandable when proliferation rather than ATP production alone is considered. A dividing cell must duplicate proteins, membranes, nucleic acids and organelles. Glycolytic and associated pathways provide carbon intermediates that can be diverted toward the pentose phosphate pathway, amino-acid synthesis, lipid synthesis and nucleotide production. This allows metabolism to support biomass production while also helping regulate reactive oxygen species and cellular redox status [4,6].

A second consequence is the accumulation and export of lactate and protons. Lactate is no longer regarded simply as metabolic waste. Within tumors it can act as a fuel, signaling molecule and regulator of stromal and immune cells. Lactate-rich, acidic regions may favor invasion, immune suppression and adaptation to stress [9-11]. This is important histologically because the tumor is not composed only of malignant cells; its vessels, fibroblasts, immune cells, extracellular matrix and areas of necrosis are part of the visible tissue pattern.

#### 3.2. Molecular regulation of aerobic glycolysis

The glycolytic phenotype can be produced by both oncogenic signaling and microenvironmental stress. Activation of growth-factor pathways, especially PI3K/AKT/mTOR signaling, increases glucose uptake and encourages anabolic metabolism. MYC can promote the expression of genes involved in glucose and glutamine metabolism, while loss of tumor suppressor functions can remove metabolic restraints. These pathways link cell-cycle stimulation with the nutrient requirements of proliferation [1,2,6].

Hypoxia-inducible factor 1 (HIF-1) is particularly important in solid tumors. HIF-1 activity rises when oxygen delivery becomes inadequate, but it may also be activated by oncogenic signaling. HIF-1 increases the expression of glucose transporters and glycolytic enzymes and induces pyruvate dehydrogenase kinase, which reduces pyruvate entry into mitochondrial oxidation. In this way, hypoxic tumor cells can maintain ATP production while reducing oxygen-dependent metabolism [12,13].

Several proteins commonly discussed in cancer metabolism can also be assessed in tumor tissues. GLUT1 facilitates glucose uptake and is overexpressed in multiple carcinomas, although expression





varies considerably among tumor types [14]. Pyruvate kinase M2 (PKM2) regulates the final steps of glycolysis and also has non-metabolic roles related to transcription and cell-cycle progression [15]. Lactate dehydrogenase A (LDHA) promotes conversion of pyruvate to lactate and has been associated with tumor growth and invasive behavior in several cancers [16]. These proteins demonstrate how biochemical reprogramming can produce measurable molecular changes within histological specimens.

### 3.3. Nuclear atypia and cellular pleomorphism

Nuclear atypia is one of the most recognizable microscopic features of malignancy. Cancer cells may show enlarged nuclei, irregular nuclear contours, hyperchromasia, abnormal chromatin distribution and an increased nuclear-to-cytoplasmic ratio. Variation in nuclear size and shape between neighboring tumor cells produces pleomorphism. These changes are used routinely in diagnosis and grading, although their molecular causes are multifactorial and include aneuploidy, chromatin alterations, nuclear-envelope abnormalities and dysregulated signaling [8].

The relationship between the Warburg effect and nuclear atypia is mainly indirect. Metabolic reprogramming supports continued proliferation and can influence epigenetic regulation through changes in the availability of metabolites used as substrates or cofactors for chromatin-modifying enzymes [2,6]. Lactate itself has also been linked to epigenetic regulation through processes such as histone lactylation. Nevertheless, it would be inaccurate to state that aerobic glycolysis directly produces pleomorphic nuclei. Nuclear abnormalities arise from the broader malignant program, while altered metabolism helps sustain the cellular state in which those abnormalities are selected and maintained.

This distinction is important in a histology-focused review. A pathologist can recognize nuclear atypia on routine sections, but cannot infer a complete metabolic phenotype from morphology alone. Tumors with similar microscopic appearances may use different metabolic pathways, and a single tumor may contain metabolically distinct cell populations.

### 3.4. Increased proliferation and mitotic activity

Malignant tumors often display increased mitotic activity. In high-grade tumors, mitotic figures may be numerous and atypical forms may occur because of abnormal chromosome segregation and defective cell-cycle checkpoints. Histological grading systems in several organs include mitotic activity as one component because it provides a practical estimate of proliferative behavior.

The Warburg effect is closely connected with proliferation because aerobic glycolysis supplies intermediates needed to build daughter cells. Vander Heiden and colleagues emphasized that proliferating cells require metabolic pathways that convert nutrients into biomass rather than maximizing ATP production alone [4]. PKM2 regulation can contribute to the accumulation of glycolytic intermediates for anabolic pathways and has also been linked with cell-cycle signaling [15]. Thus, the histological observation of abundant mitoses is compatible with the high biosynthetic demand that favors glycolytic reprogramming.

However, increased glycolysis and high mitotic counts are not interchangeable measurements. Some highly glycolytic cells may divide slowly under stress, while some tumors with active mitochondrial





metabolism may proliferate rapidly. The useful connection is functional: both are features of a biological system reorganized to sustain uncontrolled growth.

### 3.5. Loss of differentiation and tumor heterogeneity

Many malignant tumors lose some of the structural characteristics of their tissue of origin. Poorly differentiated tumors may show fewer specialized structures, altered cell polarity and a more primitive appearance. In carcinomas, gland formation or keratinization may be reduced as grade increases. Loss of differentiation is not universal, but it is a major component of histological grading in several cancers.

Metabolic reprogramming may participate in this process because metabolic pathways interact with transcriptional and epigenetic networks that regulate cell identity. Hypoxic signaling through HIF-1 can support stem-like properties and altered differentiation, and recent reviews have highlighted links among HIF-1, glycolysis, dedifferentiation and cancer stem-cell phenotypes [17]. These relationships may help explain why poorly differentiated regions of tumors often coexist with hypoxia and aggressive biological behavior.

Tumors are also metabolically heterogeneous. Cells near well-perfused vessels may have different nutrient access from cells near hypoxic or necrotic zones. Some cancer cells can oxidize lactate produced by more glycolytic neighbors. Therefore, the histological heterogeneity of a tumor may reflect not only genetic subclones but also different microenvironmental and metabolic states [2,10].

### 3.6. Hypoxia and tumor necrosis

As a solid tumor enlarges, cell growth may outpace the development of an adequate vascular network. Diffusion distances increase and regions with low oxygen and limited nutrients appear. Hypoxia activates HIF-dependent adaptation, including enhanced glycolysis and angiogenic signaling [12,13]. If metabolic adaptation is insufficient, cells in severely deprived regions die and form areas of tumor necrosis.

Necrosis is a common histological finding in many aggressive solid tumors. It may appear as eosinophilic cellular debris, loss of nuclear staining and sharply demarcated zones of dead tissue surrounded by viable tumor. Across several cancer types, the presence or extent of necrosis has been associated with unfavorable pathological features and prognosis, although its clinical value depends on tumor type and grading system [18,19].

The connection with the Warburg effect is again bidirectional rather than simple. Hypoxia encourages glycolysis, while rapid glycolytic tumor growth contributes to high nutrient consumption and microenvironmental stress. Lactate and acidity accumulate in poorly perfused regions, and cells with insufficient adaptive capacity may undergo death. Tumor necrosis is therefore a visible tissue-level sign of the competition between rapid growth, vascular supply, inflammation and metabolic stress.

### 3.7. Angiogenesis and abnormal vascular architecture

Growing tumors require access to oxygen and nutrients. HIF signaling stimulates vascular endothelial growth factor and other mediators of angiogenesis when tumor cells experience hypoxia. The resulting vessels are often structurally abnormal, with irregular branching, variable diameters, leakiness and uneven distribution. Histologically, some tumors contain prominent or atypical





microvascular patterns, and vascular density can be assessed with endothelial immunohistochemical markers [13,20].

Angiogenesis does not eliminate tumor hypoxia completely. Abnormal vessels may deliver blood inefficiently, creating a repeating pattern in which oxygen shortage activates HIF, HIF promotes angiogenesis and the newly formed vasculature remains functionally imperfect. This explains how intense vascularity and hypoxic regions can coexist in the same tumor. Lactate may also contribute to pro-angiogenic signaling within the microenvironment [10,11].

These vascular changes illustrate an important principle of cancer histology: microscopic architecture is produced by interactions between malignant cells and their surroundings. The Warburg effect influences this environment through oxygen demand, lactate production and metabolic signaling, while the vascular pattern in turn determines which metabolic pathways are most advantageous to the tumor.

### 3.8. Invasion, extracellular acidity and stromal interaction

Invasion is the defining feature that separates malignant epithelial tumors from in situ lesions. Histologically, invasive cells breach the basement membrane and grow irregularly into surrounding stroma, often accompanied by fibroblastic response, inflammation and extracellular-matrix remodeling. While invasion is fundamentally controlled by genetic and signaling changes affecting adhesion, motility and proteolysis, tumor metabolism can modify the conditions under which these processes occur.

High glycolytic activity increases lactate export and contributes to extracellular acidification. Acidic conditions can affect extracellular-matrix organization, protease activity, stromal cells and immune-cell function. Reviews of the tumor microenvironment describe lactate as a contributor to invasion, angiogenesis and immunosuppression rather than a passive waste product [9-11]. LDHA and lactate transport pathways have therefore attracted interest as potential therapeutic targets [16].

Metabolic changes have also been linked with epithelial-mesenchymal transition and stem-like states, although these relationships are context-dependent. It is safer to regard aerobic glycolysis as one supportive factor within a network that includes growth-factor signaling, matrix interactions, hypoxia and transcriptional programs. Histologically invasive growth cannot be explained by the Warburg effect alone.

### 3.9. Histological and immunohistochemical indicators of metabolic reprogramming

Routine hematoxylin and eosin staining does not directly measure glycolysis. Nevertheless, several tissue findings can suggest conditions in which metabolic reprogramming is likely to be important. These include brisk mitotic activity, high cellularity, poor differentiation, hypoxic-appearing necrotic regions and abnormal vascular patterns. None of these findings is specific for the Warburg effect.

Immunohistochemistry can provide more direct information. GLUT1 staining has been evaluated across many tumor types and shows variable membranous or cytoplasmic expression, with particularly strong expression in some squamous carcinomas [14]. HIF-1 $\alpha$ , carbonic anhydrase IX, LDHA and other metabolic proteins have also been studied as tissue biomarkers. Their interpretation, however, depends on tumor type, antibody performance, fixation, cutoff selection and intratumoral heterogeneity.



Functional imaging provides another clinical link. The high glucose uptake of many tumors is the basis of 18F-fluorodeoxyglucose positron-emission tomography. Although FDG uptake is not identical to histological grade and can occur in inflammatory tissue, it demonstrates how the basic metabolic behavior described by Warburg can be translated into a clinically useful signal.

**Table 1.** Relationship between common histological findings and metabolic processes in cancer.

| Histological feature            | Possible metabolic connection                                                                               | Important limitation                                                                        |
|---------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| High mitotic activity           | Glycolysis and associated pathways provide intermediates for biomass synthesis during rapid proliferation.  | Mitoses reflect cell-cycle activity, not glycolysis specifically.                           |
| Pleomorphism and nuclear atypia | Metabolite-dependent signaling and epigenetic regulation may support the malignant state.                   | Nuclear atypia is mainly driven by genomic, chromatin and nuclear-structural abnormalities. |
| Poor differentiation            | Hypoxia, HIF signaling and metabolic reprogramming can interact with stemness and differentiation pathways. | Differentiation is strongly tissue- and mutation-dependent.                                 |
| Necrosis                        | Rapid growth, hypoxia and nutrient deprivation create metabolic stress that can exceed adaptive capacity.   | Necrosis also depends on vascular injury, inflammation and treatment effects.               |
| Abnormal angiogenesis           | Hypoxia and HIF signaling stimulate VEGF; lactate may reinforce pro-angiogenic signaling.                   | Vascular patterns differ substantially among tumor types.                                   |
| Invasion and stromal reaction   | Lactate and extracellular acidity can influence matrix remodeling, stromal cells and immune cells.          | Invasion requires many non-metabolic signaling pathways.                                    |

#### 4. Discussion

The Warburg effect remains important because it connects cell signaling, nutrient use and the tumor microenvironment. Its historical description was relatively simple: cancer cells consume glucose and release lactate despite oxygen availability. Modern research shows a more complicated picture. Tumor cells may retain mitochondrial respiration, switch fuel sources and exchange metabolites with neighboring cells. Therefore, aerobic glycolysis is not a universal replacement for oxidative phosphorylation but one recurring metabolic strategy within malignant tissues [2,5,6].

From a histopathological perspective, the most useful interpretation is that altered metabolism helps create the conditions in which familiar malignant morphology develops. High glucose uptake and biosynthetic metabolism support rapid proliferation. Hypoxia and HIF-dependent adaptation create spatial differences within the tumor. Inadequate perfusion contributes to necrosis, while hypoxia promotes angiogenic signaling. Lactate and acidity modify immune, stromal and extracellular-matrix behavior. Together, these processes can contribute to a tissue pattern characterized by high cellularity, variable differentiation, necrosis, abnormal vessels and invasion.

Still, morphology should not be reduced to metabolism. Nuclear pleomorphism, hyperchromasia and abnormal mitotic figures are closely related to genomic instability, DNA content, chromatin organization, mitotic defects and changes in nuclear structure [8]. The Warburg effect may support



the survival and expansion of such abnormal clones, but it is not a sufficient explanation for their appearance. This distinction prevents a common oversimplification in student reviews, in which one molecular pathway is presented as the cause of nearly every characteristic of cancer.

A second important issue is heterogeneity. Not every cancer has the same degree of aerobic glycolysis. Even within one tumor, cells close to vessels may use oxidative pathways while cells farther from blood supply may depend more heavily on glycolysis. Stromal cells can also participate in metabolic exchange. Therefore, a biopsy represents both structural and metabolic heterogeneity. This helps explain why immunohistochemical markers such as GLUT1 may show uneven staining and why metabolic biomarkers do not perfectly correspond to conventional histological grade [14]. These limitations also affect therapy. Inhibiting glucose uptake, glycolytic enzymes, LDHA or lactate transport has strong biological logic, and many preclinical studies have shown antitumor effects. Yet systemic treatment is difficult because normal proliferating tissues and immune cells also use glycolysis, while tumors can adapt by using alternative nutrients and oxidative metabolism. Metabolic targeting may therefore be more effective when combined with other treatments or applied to tumors with a defined metabolic dependency rather than used as a universal anticancer strategy [2,6,16].

The topic has practical relevance for medical education because it links biochemistry with pathology. Histology often presents cancer as a set of visual criteria, while metabolism is taught separately as a biochemical pathway. In reality, these are different views of the same evolving tumor. Microscopic appearance records the consequences of proliferation, cell death, differentiation and tissue interaction; metabolic reprogramming helps supply and regulate those processes. Understanding the connection makes both subjects easier to interpret without assuming that every morphological change has one metabolic cause.

#### 4.1. Limitations of the present review

This review is narrative and was intended as an introductory synthesis rather than a systematic analysis. The included studies involve different cancer types, experimental models and methods of metabolic measurement. Direct studies that correlate metabolic flux with detailed routine histomorphology are less common than studies examining molecular pathways or individual biomarkers. As a result, several relationships discussed here are mechanistic associations rather than direct one-to-one causal links.

Another limitation is that the term Warburg effect is sometimes used broadly to describe many metabolic abnormalities in cancer. This review uses the narrower definition of increased aerobic glycolysis and lactate production while acknowledging that tumor metabolism also includes mitochondrial respiration, glutamine metabolism, lipid metabolism and metabolic cooperation between malignant and stromal cells.

#### 5. Conclusion

The Warburg effect describes the preference of many cancer cells for high glycolytic activity and lactate production even when oxygen is available. This metabolic behavior is driven by oncogenic signaling, hypoxia-related pathways and the biosynthetic requirements of proliferation. Histologically, malignant tumors may show nuclear atypia, increased mitotic activity, loss of differentiation, necrosis, abnormal angiogenesis and invasive growth. These features are not produced





by aerobic glycolysis alone, but metabolic reprogramming can support their development by sustaining rapid cell growth, helping cells adapt to hypoxia and reshaping the tumor microenvironment. The strongest visible connections are seen at the tissue level, particularly in proliferation, hypoxic-necrotic regions, angiogenesis and stromal interaction. Understanding the Warburg effect together with histological morphology provides a more integrated view of cancer biology and may help connect basic biochemical mechanisms with the appearances encountered in routine pathology.

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