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REVIEW ARTICLE

BREAST CANCER CELLS UNDER OXYGEN STRESS: ADAPTATION AND SURVIVAL MECHANISMS

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Abstract

Oxygen deprivation, or hypoxia, is a key characteristic of the tumor microenvironment in various solid tumors, such as breast cancer. As tumors exceed their blood supply, regions with low oxygen develop, generating selective pressure that fuels cancer advancement and resistance to treatment. Breast cancer cells demonstrate significant flexibility, allowing them to adjust to and endure under these difficult circumstances. Grasping the cellular and molecular reactions to hypoxia is essential for creating more efficient treatment approaches. A key adaptation to hypoxic stress includes metabolic reconfiguration. Breast cancer cells lower their dependence on oxygen driven mitochondrial respiration while boosting glycolytic activity, even when oxygen is available this is referred to as the Warburg effect. This metabolic change facilitates ATP generation and biosynthesis in oxygen-limited environments. Simultaneously, hypoxia-inducible factors (HIFs) trigger various genes related to angiogenesis, including vascular endothelial growth factor (VEGF), encouraging the development of new yet frequently ineffective blood vessels that continue to sustain hypoxic environments.
Keywords: angiogenesis, breast cancer, cell survival, hypoxia, metabolic reprogramming.

INTRODUCTION

Breast cancer is the most common cancer among women worldwide and remains a primary cause of cancer-related deaths. Its advancement and evolution are regulated not only by genetic changes and signaling modifications but also by intricate interactions with the tumor microenvironment. Among the different microenvironmental stressors, oxygen shortage referred to as hypoxia significantly influences tumor biology[1-3]. As a solid tumor grows, the pre-existing blood vessels frequently fail to satisfy the oxygen and nutrient needs of the rapidly dividing cells, resulting in the emergence of hypoxic areas within the tumor[4]. Hypoxia is not merely a passive result of tumor expansion; it plays an active role in enhancing cancer aggressiveness, resistance to therapies, and the potential for metastasis[5]. The existence of hypoxic areas in breast tumors has been linked to unfavorable outcomes, a heightened likelihood of recurrence, and resistance to standard treatments like chemotherapy and radiotherapy[6]. This results from the capacity of cancer cells to adjust to and utilize hypoxic stress via various molecular and cellular mechanisms that promote their survival and growth. A primary modulator of the hypoxic response is the hypoxia-inducible factor (HIF) family, especially HIF-1α, which functions as a transcriptional activator for many genes related to angiogenesis, metabolism, pH balance, and apoptosis[7,8].

A prominently documented response to hypoxia in breast cancer cells is the alteration of metabolism. Typically, cells depend on oxidative phosphorylation for effective ATP generation. Yet, in hypoxic conditions, cancer cells transition to glycolysis, an oxygen-independent and less efficient process, to meet their energy requirements[9,10]. This change, termed the Warburg effect, is further intensified in low-oxygen conditions, resulting in elevated glucose consumption and lactate generation. This metabolic adaptability enables cancer cells to sustain their viability and function even in areas of the tumor that lack nutrients and oxygen. Alongside modifying their metabolism, breast cancer cells trigger angiogenesis when faced with hypoxia, facilitating the creation of new blood vessels to enhance oxygen and nutrient supply. The up regulation of vascular endothelial growth factor (VEGF) driven by HIF-1α is crucial to this process. Nonetheless, the resulting blood vessels are frequently structurally and functionally irregular, causing ineffective perfusion and varying oxygen levels, which maintains a cycle of hypoxia and additional tumor adaptation[11,12]. In addition to metabolic and vascular

alterations, hypoxia impacts cellular survival pathways. Under typical conditions, oxygen stress would initiate apoptosis; nonetheless, breast cancer cells can circumvent this mechanism. By increasing the levels of anti-apoptotic proteins like BCL-2 and survivin and activating autophagy pathways, these cells can escape cell death[13,14].

The aim of this narrative review is to explore and synthesize current knowledge on the adaptive responses of breast cancer cells to oxygen stress, with a particular focus on the mechanisms by which these cells survive and proliferate in hypoxic tumor microenvironments.

The hypoxic tumor microenvironment in breast cancer

The tumor microenvironment (TME) in breast cancer is a complex and dynamic ecosystem composed of malignant cells, stromal components, immune cells, and an aberrant vasculature. As the tumor mass expands, the demand for oxygen surpasses the supply provided by the existing blood vessels, leading to the development of hypoxic regions. Hypoxia within the tumor is not uniform; instead, it exists in gradients ranging from mild to severe oxygen deprivation, depending on the distance of cells from functional blood vessels. These hypoxic zones are not merely passive byproducts of tumor growth but are active drivers of malignancy, influencing a wide array of cellular processes and contributing to tumor heterogeneity[15,16]. The primary cellular response to hypoxia is mediated by the hypoxia-inducible factors (HIFs), which function as oxygen-sensitive transcription factors. Under normoxic conditions, HIF-1α is hydroxylated by prolyl hydroxylases, leading to its ubiquitination and subsequent degradation via the von Hippel-Lindau (VHL) tumor suppressor protein. In hypoxic conditions, this hydroxylation process is inhibited, allowing HIF-1α to accumulate, dimerize with HIF-1β, and translocate to the nucleus. There, it activates the transcription of genes involved in critical survival pathways, including angiogenesis (e.g., VEGF), glycolysis (e.g., GLUT1, LDHA), erythropoiesis, and cell proliferation[17,18].

In breast cancer, persistent hypoxia applies selective pressure that promotes the survival and proliferation of more aggressive phenotypes. It is associated with improved epithelial-mesenchymal transition (EMT), an essential mechanism in metastasis, along with heightened treatment resistance. Additionally, hypoxic areas are often immunosuppressive, marked by the attraction of regulatory T cells and myeloid-derived suppressor cells, along with the suppression of cytotoxic T cell activity. This immunosuppressive setting promotes immune evasion, allowing tumor advancement[19,20]. Notably, the blood vessels in hypoxic breast tumors are typically disorganized and permeable, resulting in irregular blood flow and exacerbating oxygen shortage. This disordered vascular structure leads to recurring phases of acute and chronic hypoxia, which additionally enhance genetic instability and intra-tumor diversity. Moreover, the acidic conditions arising from anaerobic metabolism interfere with standard cell-cell and cell-matrix interactions, facilitating invasion and migration[21,22]. The clinical significance of hypoxia in breast cancer is substantial. Research indicates that gene signatures related to hypoxia correlate with worse prognosis, elevated tumor grade, and a greater chance of metastasis. Additionally, hypoxia decreases the effectiveness of radiotherapy, which depends on oxygen to produce reactive oxygen species that harm DNA. Likewise, numerous chemotherapeutic drugs are less effective in low-oxygen conditions due to modified drug metabolism and diminished growth of hypoxic cells[23].

Metabolic reprogramming in response to hypoxia in breast cancer

Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to meet the increased energetic and biosynthetic demands of rapid proliferation. In the context of hypoxia, this metabolic plasticity becomes even more pronounced. Oxygen deprivation forces breast cancer cells to shift their energy production from mitochondrial oxidative phosphorylation to glycolysis, even when oxygen is partially available. This phenomenon, known as the Warburg effect, is amplified under hypoxic conditions and is orchestrated primarily by hypoxia-inducible factors (HIFs), especially HIF-1α[24-26]. Under normal physiological conditions, cells rely on oxidative phosphorylation in mitochondria to generate adenosine triphosphate (ATP) efficiently. However, this process requires oxygen as a terminal electron acceptor in the electron transport chain. In hypoxic tumor regions, where oxygen is limited or absent, oxidative phosphorylation is compromised. HIF-1α compensates by upregulating the expression of glycolytic enzymes such as hexokinase 2 (HK2), phosphofructokinase (PFK), and lactate dehydrogenase A (LDHA). These enzymes enhance the glycolytic flux, allowing cells to generate ATP through substrate-level phosphorylation despite the reduced efficiency of the pathway[27-29].

Additionally, hypoxia induces the expression of glucose transporters, particularly GLUT1 and GLUT3, to increase glucose uptake from the extracellular environment. This adaptation ensures a continuous supply of glucose to fuel glycolysis. The end product of anaerobic glycolysis, lactate, accumulates in the tumor microenvironment, contributing to acidosis. This acidic milieu further supports tumor progression by promoting extracellular matrix degradation, angiogenesis, and immune evasion. Some breast cancer cells also express monocarboxylate transporters (MCTs), which export lactate out of the cell, helping to maintain intracellular pH homeostasis and sustain glycolytic activity[30-32].

Beyond glycolysis, hypoxic breast cancer cells exhibit alterations in other metabolic pathways, including glutaminolysis and lipid metabolism. Glutamine becomes an alternative carbon source for the tricarboxylic acid (TCA) cycle, supporting biosynthesis and redox balance. Meanwhile, lipid synthesis and storage are modulated to meet the demands for membrane biosynthesis and to buffer oxidative stress. These metabolic changes are not merely passive responses to environmental stress but are actively regulated to support survival, proliferation, and resistance to therapy[33-35]. Importantly, this hypoxia-driven metabolic rewiring provides cancer cells with a

selective advantage in the tumor microenvironment. It supports not only growth under low oxygen but also confers resistance to therapies that target rapidly dividing, oxygen-dependent cells. Moreover, metabolic flexibility allows hypoxic breast cancer cells to survive nutrient fluctuations and to outcompete less-adapted neighboring cells. Consequently, metabolic reprogramming contributes to intratumoral heterogeneity and the emergence of more aggressive subpopulations[36,37].

Angiogenesis and vascular remodeling in breast cancer

Angiogenesis the formation of new blood vessels from pre-existing vasculature is a critical adaptation that allows breast cancer cells to survive and grow in hypoxic conditions. As tumors expand beyond a certain size, diffusion becomes insufficient to deliver adequate oxygen and nutrients, leading to cellular stress. To overcome this, hypoxia triggers a well-coordinated angiogenic response primarily driven by the hypoxia-inducible factor (HIF) pathway, especially through the upregulation of vascular endothelial growth factor (VEGF). This response enables the tumor to recruit and remodel vasculature, improving perfusion and sustaining its growth[38,39]. HIF-1α plays a central role in activating the angiogenic switch under low-oxygen conditions. In breast cancer, HIF-1α stabilization leads to increased transcription of VEGF and other pro-angiogenic mediators, such as platelet-derived growth factor (PDGF), angiopoietins, and stromal-derived factor 1 (SDF-1). VEGF is a potent mitogen for endothelial cells, stimulating their proliferation, migration, and differentiation into new capillary structures. These new blood vessels aim to re-establish oxygen and nutrient delivery to the hypoxic tumor zones. However, in the context of malignancy, the angiogenesis process is often dysregulated[40,41].

Unlike the organized vasculature of normal tissues, tumor-associated blood vessels in breast cancer are typically abnormal characterized by tortuosity, leakiness, irregular diameter, and poor pericyte coverage. This aberrant vascular architecture results in uneven and inefficient blood flow, leading to areas of continued or intermittent hypoxia. Such regions create cycles of acute and chronic hypoxia, which further exacerbate tumor heterogeneity and foster a selection pressure for more aggressive cancer cell phenotypes. Moreover, the leaky nature of tumor vasculature facilitates tumor cell intravasation into the bloodstream, promoting metastasis[42,43]. Vascular remodeling in breast cancer involves not only the formation of new vessels but also the alteration of existing vascular networks. Hypoxia stimulates the recruitment of endothelial progenitor cells (EPCs) from the bone marrow, contributing to neovascularization.

Additionally, tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs) within the tumor microenvironment secrete angiogenic factors that amplify vascular growth and remodeling. This crosstalk between cancer cells and stromal components is essential for sustaining the pro-angiogenic state and maintaining tumor vascular plasticity[44].

Angiogenesis also interacts with other hypoxia-driven processes such as metabolism, immune modulation, and extracellular matrix remodeling. For instance, the acidic microenvironment created by lactate accumulation can enhance VEGF production and endothelial cell migration. Moreover, VEGF itself exerts immunosuppressive effects by inhibiting dendritic cell maturation and promoting the expansion of regulatory T cells, further contributing to immune evasion in the hypoxic tumor niche[45]. Targeting angiogenesis has been a focus of therapeutic strategies in breast cancer. Anti-VEGF agents, such as bevacizumab, have shown efficacy in reducing tumor vascularization and improving progression-free survival in some breast cancer subtypes. However, clinical benefits have often been transient and modest, partly due to compensatory angiogenic pathways and the persistence of hypoxia. Additionally, excessive pruning of blood vessels can paradoxically worsen hypoxia, enhancing tumor aggressiveness and therapeutic resistance[46].

Evasion of apoptosis and enhanced survival in breast cancer

In healthy tissues, cells experiencing severe stress such as nutrient deprivation, DNA damage, or hypoxia typically undergo programmed cell death, or apoptosis, as a protective mechanism to maintain tissue integrity. However, breast cancer cells exposed to hypoxic conditions often evade apoptosis through a range of adaptive mechanisms that promote survival and continued tumor progression. These adaptations are not incidental but are actively regulated through both transcriptional and post-translational modifications, largely orchestrated by hypoxia-inducible factors (HIFs), particularly HIF-1α[47,48]. Under hypoxic stress, HIF-1α alters the balance of pro-apoptotic and anti-apoptotic signaling pathways to favor cell survival. One key adaptation involves the upregulation of anti-apoptotic proteins such as B-cell lymphoma 2 (BCL-2), BCL-XL, and survivin. These proteins inhibit the mitochondrial pathway of apoptosis by preventing cytochrome c release and caspase activation, effectively blocking cell death. At the same time, hypoxia can suppress the expression or activity of pro-apoptotic factors like BAX, PUMA, and BID, further tipping the balance toward survival. This altered apoptotic threshold allows breast cancer cells to persist and even thrive in hostile microenvironments that would be lethal to normal cells[49-51].

Autophagy, a self-digestive cellular process, also plays a critical role in the survival of hypoxic breast cancer cells. When oxygen and nutrient availability are limited, autophagy is upregulated as a protective mechanism to recycle cellular components and maintain metabolic homeostasis. HIF-1α and AMP-activated protein kinase (AMPK) pathways contribute to this process by inducing genes involved in autophagosome formation and lysosomal degradation. While autophagy can act as a form of programmed cell death under certain conditions, in hypoxic breast tumors it is more commonly associated with cytoprotective functions that support cell viability and resistance to therapy[52-54]. Additionally, breast cancer

cells under hypoxia often exhibit alterations in the p53 signaling pathway. The tumor suppressor protein p53 is a major regulator of apoptosis and cellular stress responses. In many breast cancers, p53 is mutated or functionally inactivated, allowing cancer cells to bypass p53-dependent apoptotic mechanisms. Even in tumors with wild-type p53, hypoxia can impair its transcriptional activity, reducing the expression of downstream pro-apoptotic targets. This impairment of p53 function under hypoxic conditions represents another critical node of apoptosis evasion[55-57].

The hypoxic microenvironment also fosters the development of cancer stem-like cells (CSCs), which possess enhanced survival capabilities and are more resistant to apoptosis. These CSCs are thought to be responsible for tumor recurrence and metastasis, in part due to their quiescent nature and heightened expression of survival proteins. Hypoxia supports the maintenance and self-renewal of these cells through HIF-mediated signaling, including activation of Notch, Wnt, and Hedgehog pathways all of which are associated with stemness and survival[58,59]. The ability of breast cancer cells to evade apoptosis under hypoxic conditions contributes significantly to treatment resistance. Radiotherapy and many forms of chemotherapy rely on the induction of DNA damage and subsequent apoptotic cell death. Hypoxic cells, with their suppressed apoptotic machinery and enhanced repair capabilities, are less responsive to these interventions. This underscores the need for therapeutic strategies that can restore apoptotic sensitivity or exploit alternative forms of cell death in hypoxic tumor cells[60].

Therapeutic implications in breast cancer

The presence of hypoxia within the breast tumor microenvironment presents a major challenge to conventional cancer therapies, but it also offers opportunities for novel, targeted interventions[61]. Hypoxia-induced adaptations such as metabolic reprogramming, angiogenesis, and resistance to apoptosis not only enable tumor survival and progression but also confer resistance to chemotherapy, radiotherapy, and hormonal treatments[61,62]. One therapeutic avenue involves the inhibition of hypoxia-inducible factors (HIFs), particularly HIF-1α, which acts as a master regulator of the cellular hypoxic response. Preclinical studies have demonstrated that HIF-1α inhibition can reduce tumor angiogenesis, sensitize breast cancer cells to radiation, and suppress metastasis. Small-molecule inhibitors of HIF-1α, such as PX-478, are currently under investigation and have shown promising anti-tumor activity in early-phase clinical trials. However, due to the complexity and redundancy of hypoxia signaling pathways, targeting HIFs alone may not be sufficient in all tumor contexts[63,64]. Another promising strategy targets the altered metabolism of hypoxic breast cancer cells. Glycolytic inhibitors, such as 2-deoxy-D-glucose (2-DG), and lactate transport inhibitors targeting monocarboxylate transporters (MCTs) are being explored to disrupt energy production in hypoxic cells. Similarly, drugs that modulate mitochondrial function or block glutamine metabolism may selectively impact hypoxia-adapted cancer cells. Importantly, these agents may enhance the efficacy of standard therapies by sensitizing hypoxic cells that are otherwise resistant[65,66].

Angiogenesis inhibitors, such as the anti-VEGF monoclonal antibody bevacizumab, have been tested in breast cancer with mixed results. While they can transiently normalize tumor vasculature and improve drug delivery, long-term use may paradoxically exacerbate hypoxia by excessively pruning blood vessels. Combining angiogenesis inhibitors with chemotherapy, immunotherapy, or metabolic modulators may offer a more balanced and effective therapeutic approach[67,68]. Efforts to re-sensitize hypoxic tumor cells to apoptosis have also gained traction. BH3 mimetics, which inhibit anti-apoptotic BCL-2 family proteins, are under investigation in combination with other agents to overcome apoptosis resistance in hypoxic breast tumors. Moreover, autophagy inhibitors such as chloroquine have shown potential in disrupting hypoxia-induced survival pathways, particularly when used in combination with chemotherapy or radiotherapy[69,70]. Recent advances in immunotherapy also hold promise for overcoming hypoxia-associated immune evasion. Hypoxia can suppress immune surveillance by impairing cytotoxic T cell activity and promoting an immunosuppressive milieu. Strategies to reverse these effects include the use of immune checkpoint inhibitors alongside agents that normalize the tumor vasculature or modulate the tumor's metabolic landscape. Targeting the hypoxic niche may thus enhance the efficacy of immunotherapeutic regimens in breast cancer, particularly in more aggressive or treatment-refractory subtypes[71,72].

CONCLUSIONS

Breast cancer cells exhibit extraordinary flexibility when facing oxygen deprivation, employing various survival strategies to flourish in the low-oxygen tumor microenvironment. These adaptations—comprising metabolic reprogramming, angiogenesis, resistance to apoptosis, and immune escape play a role in tumor progression, therapeutic resistance, and unfavorable clinical results. Hypoxia, rather than merely being a passive effect of tumor proliferation, serves as a key promoter of cancer by altering cellular behavior and affecting relationships within the tumor microenvironment. It offers understanding of treatment failure mechanisms and emphasizes potential new paths for therapeutic intervention.

Focusing on pathways that respond to hypoxia, like HIF signaling, glycolytic metabolism, angiogenesis, and apoptosis resistance, shows potential for addressing therapy resistance and enhancing the effectiveness of both traditional and novel treatments, including immunotherapy.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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