

Roles of oxygen in the tumorigenesis, progression, and treatment of breast cancer

Costel C. Darie^{1,*}, Angiolina Hukovic¹, Veronica D. Maynard¹, Anca-Narcisa Neagu^{2,*}

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Abstract

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death among women worldwide. Poor prognosis in breast cancer patients is often linked to the presence of intratumoral hypoxic areas caused by abnormal vascularization and insufficient oxygen availability, which results in energetic crisis in cancer cells; metabolic and epigenetic reprogramming; the transcription of genes involved in angiogenesis; cancer cell proliferation; increased motility, aggressiveness and metastasis; the accumulation of mutations; genomic instability; the maintenance of stem cell characteristics; stromal cell recruitment; extracellular matrix remodeling; chronic inflammation; immune evasion; and adaptive responses in the tumoral microbiota. Furthermore, hypoxia is often correlated with resistance to traditional antitumor treatments used alone or in combination, which results in the need to implement novel therapies to overcome or alleviate the negative effects of oxygen deprivation in breast cancer therapeutics. In breast cancer modeling research, micro- and nanofabrication-based technologies, including breast cancer-on-chip and breast cancer metastasis-on-chip platforms, are able to recapitulate the metastatic cascade of breast cancer in different controlled oxygen gradients. Mass spectrometry-based proteomics, including mass spectrometry imaging, offers opportunities for detecting, quantifying and understanding the roles of proteins and peptides, protein-protein interaction networks, and posttranslational modifications of proteins involved in hypoxia-associated biopathological processes. In this mini-review, we have summarized several modern approaches that are able to overcome the undesirable effects of hypoxia for breast cancer treatment. Thus, natural compounds with inhibitory effects on hypoxia-related signaling pathways in breast cancer cells and the tumor microenvironment, hyperbaric oxygen therapy, viral vector-based therapy that uses genetically engineered oncolytic viruses, and oncological bacteriotherapy based on biohybrid platforms, including anaerobic bacteria that are able to colonize inaccessible hypoxic regions in breast tumors to deliver chemotherapeutic drugs just into the tumor site, and smart nanoplatforams for abundant O₂ generation within hypoxic breast cancer areas, including erythrocyte-like nanoparticles, metal-organic framework-nanoparticles, or engineered microalgae-metal-organic framework oxygenators, have been designed to relieve tumor hypoxia, induce antitumor responses, and improve the effects of traditional anti-breast cancer therapies.

Key Words: breast cancer; cancer progression; cancer therapy; oxygen; tumorigenesis

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer death among women worldwide. Carcinogenesis, tumor progression, resistance to anticancer treatments, and poor prognosis in BC patients are closely linked to the presence of intratumoral hypoxic areas that dynamically change at the spatiotemporal level due to transient, cycling or intermittent imbalance between the high metabolic rate of cancer cells and aberrant angiogenesis, which leads to abnormal vascularization of tumors and is unable

to assure an appropriate oxygenation status and the diffusion of oxygen into tumor cells and the tumor microenvironment (TME). Thus, hypoxia is a key hallmark of most cancer types and can also model or cause other hallmarks.¹ Many types of tumor hypoxia have been described on the basis of heterogeneity of blood vessel networks and insufficient oxygen availability, which results in energetic crisis in cancer cells; transcription of genes promoting excessive angiogenesis in primary tumors; maintenance of stem cell characteristics; accumulation of

genomic instability and mutations; cancer cell proliferation and motility; local invasion and distant metastasis; stromal cell recruitment; extracellular matrix remodeling; maintenance of chronic permanent inflammation; immune evasion; adaptive response in the intratumoral microbiota; and the requirement of hundreds of biochemical reactions (Figure 1).²⁻⁵ Additionally, hypoxia is linked with other forms of cellular stress, such as extracellular acidosis, lactate accumulation, adenosine accumulation, and glucose deprivation.¹

¹Biochemistry & Proteomics Laboratories, Department of Chemistry and Biomolecular Science, Clarkson University, Potsdam, NY, USA; ²Laboratory of Animal Histology, Faculty of Biology, "Alexandru Ioan Cuza" University of Iasi, Iasi, Romania

*Correspondence to: Costel C. Darie, PhD, cdarie@clarkson.edu; Anca-Narcisa Neagu, PhD, aneagu@uaic.ro.

<https://orcid.org/0000-0001-6402-2311> (Costel C. Darie); <https://orcid.org/0000-0002-1026-8209> (Anca-Narcisa Neagu)

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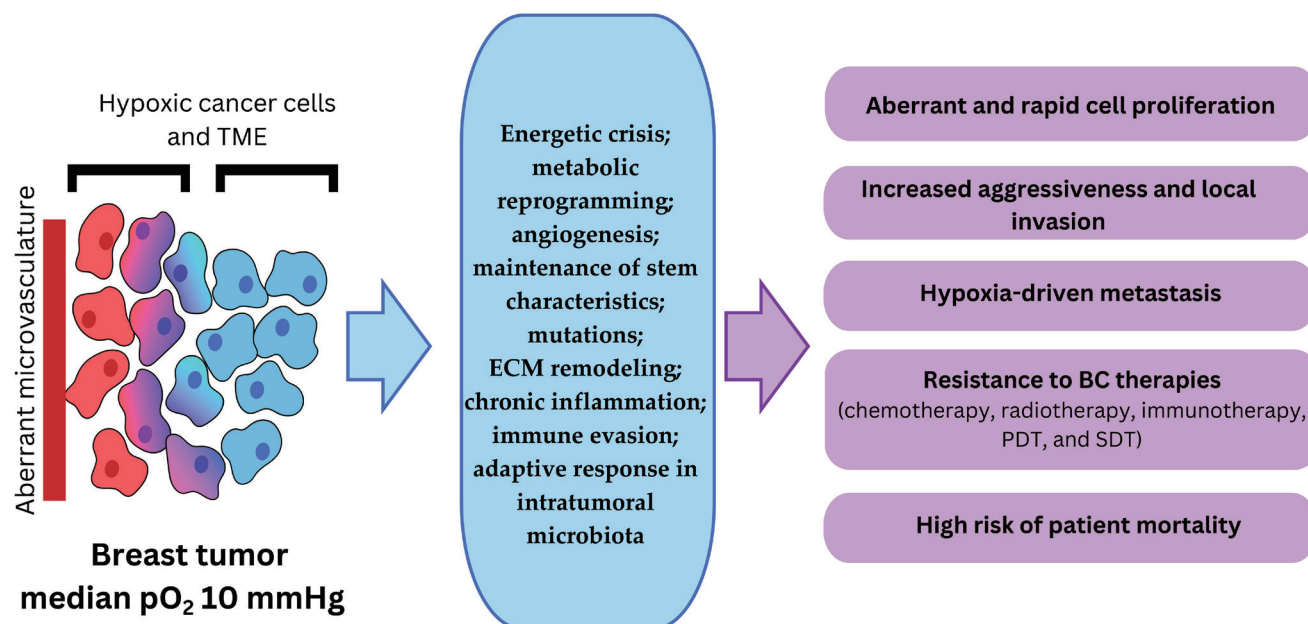


Figure 1 | Effects of hypoxia on the progression of BC.

BC: Breast cancer; ECM: extracellular matrix; PDT: photodynamic therapy; pO₂: partial pressure of oxygen; SDT: sonodynamic therapy; TME: tumor microenvironment.

Studies mentioned in this review were searched in the PubMed database using these keywords: “breast cancer, cancer progression, cancer therapy, oxygen, tumorigenesis.” All years were included in the search.

Ischemic hypoxia, also called acute hypoxia, is due to transient perfusion-limited oxygen delivery; diffusion-limited hypoxia, also known as chronic hypoxia, is caused by increased diffusion distances between the microvasculature and tumor cells, whereas tumor-associated or anemic hypoxia leads to a reduced oxygen transport capacity of the blood.⁶ Intratumoral hypoxia occurs in 90% of solid tumors and is associated with a high risk of metastasis and patient mortality.⁷ Forty percent of BCs emphasize hypoxic tissue areas.⁸ The level of molecular oxygen (O₂) in tissues is usually reported as the concentration of oxygen ([O₂]) or as the partial pressure of oxygen (pO₂), with a known relationship between them.⁹ Healthy breast tissue is reported to have [O₂] greater than 9% or a mean pO₂ of 65 mm Hg, with no pO₂ levels below 12.5 mmHg.^{6,8} Sixty percent of BCs investigated by Vaupel et al.⁶ had pO₂ values ≤ 2.5 mmHg, whereas one-third of tumors reported by Chun et al.⁸ had regions where [O₂] was ≤ 0.3%. The reported median [O₂] in hypoxic regions of breast tumors is 3.9%, whereas the median pO₂ value is 10 mmHg. Oxygen deprivation triggers metabolic reprogramming and angiogenesis to increase BC cell growth, aberrant and rapid cell proliferation, aggressiveness, hypoxia-driven cancer metastasis and resistance to different types of BC therapy, including chemotherapy, radiotherapy, immunotherapy, photodynamic therapy (PDT),

and sonodynamic therapy (SDT), which are all negatively impacted by oxygen deprivation.^{6,8} Published proteomics-based data suggest that basal-like BC cells might have a chronic hypoxia-like phenotype compared with luminal-like cells.¹⁰

The family of hypoxia-inducible factor (HIF) transcription factors (TFs) are central regulators that adapt the cellular response to low oxygen availability in the environment and are overexpressed and activated in BC.¹¹ Over 1500 HIF target oncogenes and tumor suppressor genes are involved in adapting cells to low-oxygen conditions, as are several hundred proteins involved in HIF1α-related pathways, which are involved mainly in the HIF1α interactome, such as tumor suppressor protein p53, GATA3, β-catenin, epithelial-to-mesenchymal transition-inducing TFs, nuclear factor-κB, c-Myc, signal transducer and activator of transcription family members, steroid hormone receptors, the forkhead-box family of TFs (FOXs), YAP/TAZ/TEADs and many others, which are significantly deregulated in response to TME hypoxia.⁷ Posttranslational modifications of TFs in the HIF1α interactome are crucial regulatory mechanisms that drive cell responses to BC hypoxia.¹² Hypoxia also modulates histone posttranslational modifications and the levels of HIF isoforms.¹³ Thus, epigenetic reprogramming under conditions of hypoxic exposure has a great impact on metabolic rewiring, hormone signaling, cancer stemness, and ion dynamics, emphasizing the significant therapeutic potential of targeting hypoxia in BC.¹⁴ HIF1α-related proteins recruit epigenetic regulators, such as Na⁺ and Ca²⁺ ions, which play key roles in BC progression, to control

the expression of target genes and regulate major signaling molecules involved in a range of cellular responses to hypoxia.¹⁴ In BC, as in other solid tumors, oxygen deprivation can also lead to long-lasting “hypoxic memory” imprinted on the genome, transcriptome, proteome and phenotype of posthypoxic cancer cells, even if they intravasate as circulating tumor cells and reoxygenate in the blood, leading to the maintenance of a reduction in or suppression of tumor-intrinsic type I interferon signaling, which influences both tumor cells and the TME, and the dysregulation of other pathways associated with the persistence of a more invasive behavior of cells in luminal BC during the colonization of distant metastatic sites into target organs.¹⁵ Entinostat, a histone deacetylase inhibitor, can erase hypoxia and improve the efficacy of the antigen presentation machinery for immune clearance in BC cells.

HIF1α promotes BC metastasis to axillary lymph nodes, bone colonization by BC cells, and BC metastasis to the lungs.⁷ In cancer modeling research, recent advancements in micro- and nanofabrication technologies and diverse biomaterials and nanorobots have allowed the development of many varieties of BC-on-chip or BC metastasis-on-chip platforms that incorporate multiple BC cell lines derived from human breast tissues, emphasizing different degrees of malignancy, and three-dimensional microvascular network systems or 3D native bone matrices to study BC metastatic colonization to the bone hypoxic microenvironment, which are emerging as reliable *in vitro* tools that recapitulate

the biopathopathological processes involved in the BC metastatic cascade, such as migration, angiogenesis, intravasation, extravasation, and metastatic colonization of targeted organs in different controlled oxygen gradients.¹⁶ Moreover, microfluidic chip platforms offer evidence that HIF1 α is essential for promoting aggressive behavior according to the degree of malignancy of different BC cell lines, such as MCF7 and MDA-MB-231.¹⁶ Additionally, recent advances in mass spectrometry-based proteomics have offered great opportunities for detecting and understanding the role of HIF1 α protein–protein interaction (PPI) networks and posttranslational modifications of HIF1 α and HIF1 α -associated molecular players, which drive BC tumorigenesis, development and resistance to radiation or chemotherapy. Matrix-assisted laser desorption/ionization-mass spectrometry can be used to map the spatial distribution of hypoxic areas as well as hypoxia-regulated proteins and lipids involved in glycolysis and glucose metabolism, protein folding, the spliceosome, translation/ribosome, the FAS signaling pathway, protein processing in the endoplasmic reticulum, actin cytoskeleton reorganization, the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin signaling pathway, the RAS signaling pathway, detoxification of reactive oxygen species, apoptosis, and telomere stress-induced senescence in breast tumor tissue samples.¹⁷ Moreover, the matrix-assisted laser desorption/ionization-mass spectrometry approach is able to identify specific proteins that are overexpressed in hypoxic areas of breast tumors, such as cathepsin D, which is bound to the extracellular matrix in BC, and serpin family H member, which specifically binds to collagen and can act as a chaperone in the collagen biosynthetic pathway in BC.¹⁷ The discovery of novel putative biomarkers, such as cathepsin D and serpin family H member, shows that the hypoxic TME is a driving force for BC progression.⁷

BC hypoxia is often correlated with resistance to antitumor treatments.³ Drug efflux, hypoxia-driven tumor stem cell enrichment, autophagy, and apoptosis are the most important signaling pathways involved in the HIF1 α -modulated resistance of different BC subtypes, including triple-negative BC, to a range of conventional chemotherapeutic approaches.⁵ The use of HIF1 α inhibitors, such as digoxin and vinorelbine, as targeted HIF1 α -related chemotherapies in clinical trials has not achieved the expected results.¹¹ Moreover, hypoxia promotes resistance to taxane-related antineoplastic agents, such as paclitaxel and docetaxel, which are involved in microtubule dynamics to dysregulate spindle fiber formation and cell division, as well as resistance to radiotherapy and anti-PD-1

immunotherapy.¹⁴ The *ESR1* gene, which encodes estrogen receptor alpha, can be silenced by hypoxia, with implications for estrogen receptor alpha expression and the resistance of BC cells to antiestrogen therapy.¹⁴ PDT efficacy is also significantly reduced by hypoxia in the TME because PDT generates reactive oxygen species, which require high oxygen consumption.¹⁸ SDT necessitates combination with chemotherapy within oxygen-loaded nanoplatforms to overcome hypoxia and enhance the efficacy against BC.¹⁹ In oncological viral vector-based therapy, attenuated and genetically engineered oncolytic viruses, such as herpes simplex virus, have been produced for precise targeting of hypoxic BC cells through the placement of key viral genes under the regulation of a hypoxia-responsive enhancer that is selectively overexpressed within hypoxic tissue.⁸ In oncological bacteriotherapy, anaerobic bacteria, i.e., *Bifidobacterium infantis*, and bovine serum albumin nanoparticles (NPs) can be incorporated into bacteria-based biohybrid platforms that are able to colonize inaccessible hypoxic regions in breast tumors, where they deliver doxorubicin drugs that accumulate at the tumor site.²⁰ To overcome and improve the low efficacy of targeted HIF1 α -related chemotherapy in BC treatment, novel drug delivery systems and other combination treatments that specifically target hypoxic areas in breast tumors have been designed (**Figure 2**).¹¹ Drug delivery systems can include liposomal nanoparticles, which contain encapsulated anticancer drugs, i.e., acriflavine, which is able to inhibit the HIF pathway, native and synthetic polymer NPs, which incorporate anticancer drugs, curcumin or betulinic acid micelles, metal nanomaterials that can direct drugs into a specific tissue under the action of an external magnetic field, and carbon-based NPs with specific optical and electrical properties.¹¹ NPs used in drug delivery systems have many advantages in BC treatment, such as high bioavailability, permeability, and biodegradability; the capacity to be loaded with and deliver multiple drugs that address breast tumor heterogeneity; and a high capacity to preserve healthy cells and tissues due to their nontoxicity or decreased cytotoxicity. Oxygenation of BC regions under hypoxia alleviates the main effects of hypoxia, which enhances tumor aggressiveness, restricts the efficacy of antitumor therapies, and overcomes, at least in part, the negative effects of cancer therapies. To overcome the undesirable effects of hypoxia for BC treatment, nanotechnology and nanomedicine are also valuable nanosolutions that use NP-based oxygen-enhancing agents that convert peroxide (H₂O₂) at tumor sites to produce O₂ and H₂O.²¹ Thus, to enhance the effects of chemo- and PDT-based therapies in cancer, pH-responsive, oxygen self-

sufficient, smart nanoplatforms that are effective for oxygen generation and the mitigation of hypoxia in the TME have been designed.²² These platforms integrate hollow mesoporous silica NPs loaded with doxorubicin as a chemotherapeutic drug, chitosan, which responds to the weakly acidic TME and releases drugs in a controllable manner, and chlorin e6 and catalase, which decompose endogenous hydrogen peroxide in situ, generating oxygen.²² Furthermore, systemic administration of artificial erythrocyte-like NPs, which combine discoidal mesoporous silica NPs with an erythrocyte membrane that releases drugs similar to natural red blood cells, can effectively relieve tumor hypoxia and improve the efficacy of chemotherapy.²³ Metal-organic framework (MOF)-derived titanium oxide NPs,²⁴ or MnO₂-decorated porphyrin-based Zr-MOF NPs incorporated into a chitosan hydrogel to enhance stability and retention at the tumor site,²⁵ have been used to relieve tumor hypoxia or as immune boosters that can improve the effects of immunotherapy through immunogenic cell death and TME remodeling, making them promising agents for cancer therapy. Among other therapeutic effects, these functionalized NPs can effectively convert H₂O₂ into O₂ in the TME, ultimately eliminating primary tumors via PDT/photothermal therapy under near-infrared light irradiation.^{24,25} Recently, different oxygenators for abundant O₂ generation through engineered microalgae-mediated photosynthesis, such as Chl-MOF, which contains *Chlorella vulgaris* modified with MOF-NPs, have been engineered to alleviate BC tumor hypoxia.²⁶ Biological materials have many advantages, including high tumor-targeting ability, high proactive mobility, ability to act as microswimmers, deep penetration capability for efficient drug delivery, low or no cytotoxicity, high biocompatibility, enhanced macrophage phagocytic activity and immune cell infiltration. Thus, Chl-MOF oxygenators can induce a strong antitumor immune response and have been developed for synergistic PDT-SDT and immunotherapy in BC.²⁶ Tumor oxygenation can also be induced by innovative nitric oxide gas-assisted cancer photothermal therapy, in which nitric oxide gas sensitizes tumor cells to photothermal therapy-induced hyperthermia by inhibiting protective autophagy, reducing heat resistance through heat shock protein modulation, and promoting apoptosis and the antitumor immune response.²⁷ Moreover, several natural compounds that are less toxic and have fewer side effects than standard chemotherapeutic drugs have emerged as promising anti-BC compounds. Thus, honokiol from *Magnolia* plants has been reported to exert inhibitory effects on HIF1 α and hypoxia-related signaling pathways in BC cells, mainly by enhancing HIF1 α ubiquitination

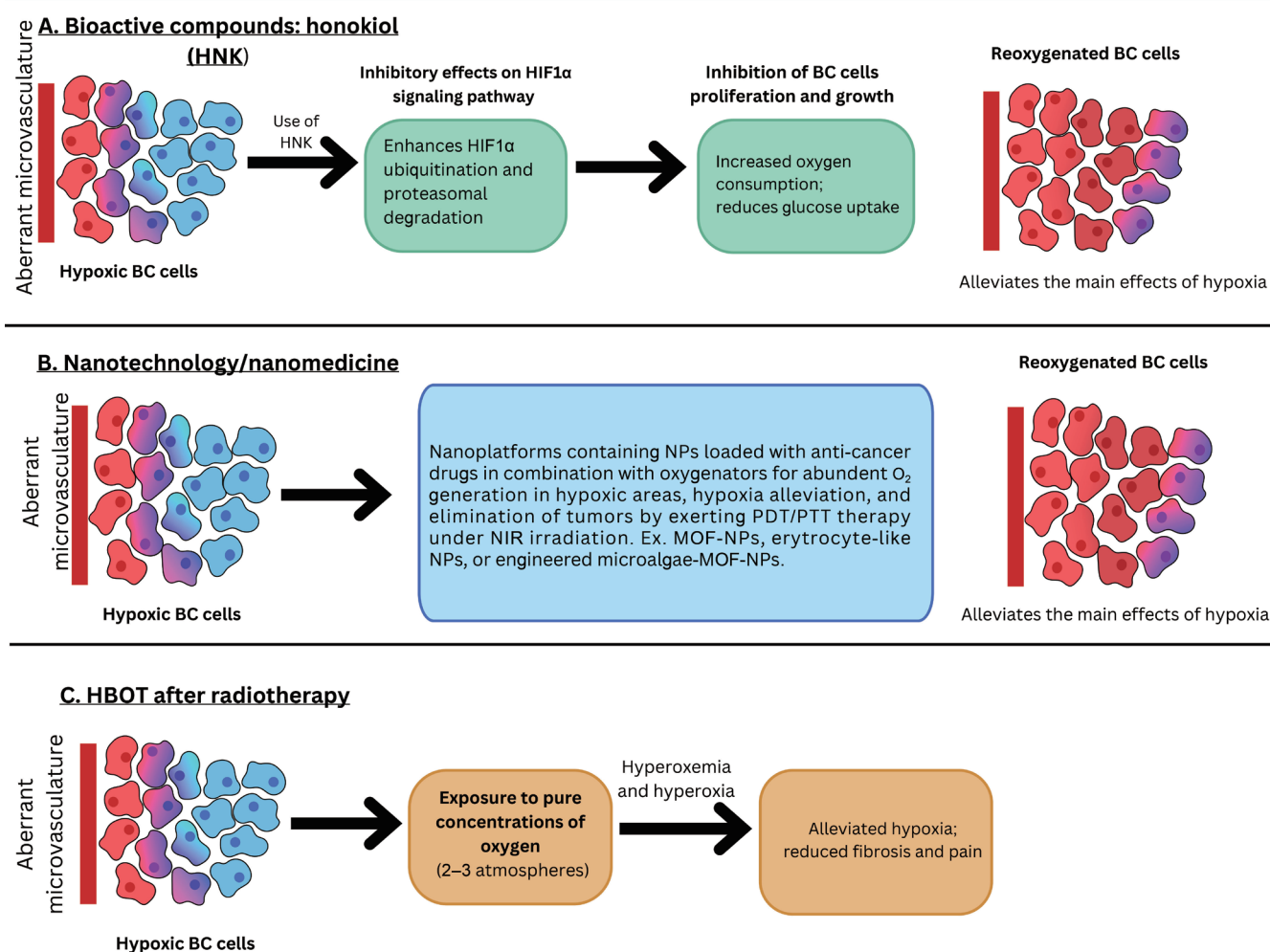


Figure 2 | Proposed solutions to alleviate hypoxia/symptoms.

(A) Honokiol inhibits HIF1 α , resulting in the inhibition of BC cell proliferation. (B) Nanotechnology based on NPs and oxygenators for targeting tumor sites and delivering anticancer drugs. (C) HBOT has been shown to decrease pain and fibrosis in BC patients receiving radiotherapy. BC: Breast cancer; HBOT: hyperbaric oxygen therapy; HIF1 α : hypoxia inducible factor 1 α ; MOF: metallic organic framework; NIR: near-infrared light; NPs: nanoparticles; PDT: photodynamic therapy; PTT: photothermal therapy; SDT: sonodynamic therapy.

and its proteasomal degradation, followed by downregulation of HIF1 α and its downstream regulators.²⁸ Honokiol increases the oxygen consumption rate and reduces glucose uptake and lactic acid and ATP production in BC cells, and the inhibitory effect on glycolysis is HIF1 α dependent, resulting in the inhibition of BC cell proliferation.²⁸ Finally, hyperbaric oxygen therapy ensures exposure to pure concentrations of oxygen at 2–3 atmospheres, leading to hyperoxemia and hyperoxia to counteract hypoxic effects in the TME, induce neovascularization and reduce fibrosis and pain; thus, hyperbaric oxygen therapy was proposed as a treatment for late radiation toxicity after adjuvant radiotherapy for BC patients.²⁹

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