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REVIEW

Research progress in tumor angiogenesis and drug resistance in breast cancer

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ABSTRACT Angiogenesis is considered a hallmark pathophysiological process in tumor development. Aberrant vasculature resulting from tumor angiogenesis plays a critical role in the development of resistance to breast cancer treatments, *via* exacerbation of tumor hypoxia, decreased effective drug concentrations within tumors, and immune-related mechanisms. Antiangiogenic therapy can counteract these breast cancer resistance factors by promoting tumor vascular normalization. The combination of antiangiogenic therapy with chemotherapy, targeted therapy, or immunotherapy has emerged as a promising approach for overcoming drug resistance in breast cancer. This review examines the mechanisms associated with angiogenesis and the interactions among tumor angiogenesis, the hypoxic tumor microenvironment, drug distribution, and immune mechanisms in breast cancer. Furthermore, this review provides a comprehensive summary of specific antiangiogenic drugs, and relevant studies assessing the reversal of drug resistance in breast cancer. The potential mechanisms underlying these interventions are discussed, and prospects for the clinical application of antiangiogenic therapy to overcome breast cancer treatment resistance are highlighted.

KEYWORDS Angiogenesis; breast cancer; chemotherapy; drug resistance; vascular normalization; immunologic therapy; tumor microenvironment (TME)

Introduction

Breast cancer is currently the most prevalent type of cancer among women[1], and its incidence is increasing every year[2]. Breast cancer treatments include primarily endocrine therapy, surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, which function by mobilizing the autoimmune system. With advancements in therapeutic drugs and the development of auxiliary detection methods, the 5-year survival rate of patients with breast cancer has increased. Nevertheless, drug resistance in breast cancer decreases the patient survival rate; consequently, breast cancer remains the leading cause of cancer death among women worldwide[3]. Investigating the mechanisms underlying drug resistance in breast cancer and developing novel treatment strategies will be crucial to reverse drug resistance during breast cancer treatment.

Drug resistance in breast cancer is associated with factors including apoptosis, ferroptosis, drug efflux systems, and tumor angiogenesis. Angiogenesis is considered a marker of tumor growth. Normal blood vessels serve as conduits for the delivery of oxygen and nutrients. Tumor angiogenesis, the formation of morphologically abnormal blood vessels from the existing capillaries or postcapillary venules, results in the development of an immature vascular network. These newly formed vessels have extremely thin walls and lack smooth muscle components, thus hindering proper oxygen delivery and drug transport during tumor treatment. When the diameter of the tumor is > 0.5 mm, the oxygen obtained by tumor cells *via* simple diffusion is insufficient to support cell growth. Therefore, tumor cells rely on angiogenesis to obtain more oxygen and maintain growth. Tumor angiogenesis leads

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to disordered internal tumor vasculature and aggravation of hypoxia, which in turn directly promotes the transcription of drug-resistance genes such as *Multi-drug Resistance Protein1* (*MDR1*), *Multi-drug Resistant Associate Protein1* (*MRP1*), and *Breast Cancer Resistance Protein* (*BRCP*)[4,5]. Concurrently, tumor angiogenesis affects drug distribution, and alters the immune system both inside and outside tumors[6]. Vascular endothelial growth factor (*VEGF*) is highly expressed in tumor angiogenesis and binds *VEGF* receptor (*VEGFR*), thereby preventing antigen presentation and inhibiting T-cell activation. Simultaneously, angiogenesis-related factors induce macrophage polarization toward the M2 phenotype, thereby leading to the development of an immunosuppressive tumor microenvironment (TME). These factors directly or indirectly contribute to the occurrence of tumor drug resistance. Notably, tumor angiogenesis plays a crucial role in the occurrence of drug resistance in breast cancer. Anti-tumor angiogenesis increases the normalization of blood vessels, inhibits tumor hypoxia and the immunosuppressive TME, increases the effective drug concentrations in tumors, and enhances drug efficacy. Therefore, anti-angiogenesis therapy can be used to reverse drug resistance in breast cancer[7].

Tumor vascular normalization, a novel angiogenesis-specific concept for the treatment of tumors, was first proposed by R. K. Jain in 1974. Targeting *VEGF* or hypoxia-inducible factor (*HIF-1*) can help normalize the tumor blood vessels, promote drug delivery, improve tumor hypoxia and the immunosuppressive microenvironment[8], and ultimately prevent or reverse drug resistance in breast cancer. This review describes the mechanisms underlying angiogenesis and drug resistance in breast cancer, and explores the possibility of reversing drug resistance *via* vascular normalization. The efficacy of a single anti-angiogenesis targeted agent on the inhibition of tumor growth is short-lived[9]. Investigating the relationship between angiogenesis and drug resistance in breast cancer, and the combination of anti-angiogenic and vascular normalization, may provide novel ideas for reversing drug resistance in breast cancer.

Mechanism of angiogenesis

Tumor angiogenesis involves the activation of transcription factors, such as *HIF-1α*, within the hypoxic tumor environment. This activation leads to the proliferation and migration of endothelial cells, as mediated by growth factors such as *VEGF* and *Platelet-derived Growth Factor* (*PDGF*), thus resulting in the formation of a complicated and disordered tumor vasculature.

Classical growth factors

VEGF and VEGFR

The discovery of *VEGF* has greatly advanced understanding of tumor angiogenesis and enabled its potential targeting in cancer therapy. The binding of *VEGF-A* to *VEGFR2* is crucial for angiogenesis. Notably, *VEGF-A* binding leads to the tyrosine phosphorylation of *VEGFR2*, which in turn further activates downstream signaling pathways including the *MAPK* and *PI3K* pathways. Furthermore, pathways such as *PLCγ*[10], *ERK1/2*, and *PI3K*[11] stimulate endothelial cell division. The activation of *endothelial nitric oxide synthase* (*eNOS*)[12] increases vascular permeability[13] (**Figure 1**). A recent study has revealed that *VEGF* inhibition effectively inhibits tumor angiogenesis, promotes vascular normalization, and inhibits tumor growth[14]. Nevertheless, the normalization of blood vessels by targeting *VEGF* anti-tumor angiogenesis therapy is short-lived. Therefore, investigating the appropriate dose and time window of drugs to promote and maintain tumor vascular normalization may become a primary focus of future research on anti-tumor angiogenesis[15].

PDGF and PDGF receptor (PDGFR)

PDGF is a growth factor that is secreted by platelets and their stromal cells and is involved in the regulation of angiogenesis. This growth factor comprises the following 4 subunits: *PDGF-A*, *PDGF-B*, *PDGF-C*, and *PDGF-D*[16]. *PDGFR* is divided primarily into *PDGFR-α* and *PDGF-β*. Studies have focused on the binding between *PDGF-B* and *PDGFR-β*, and subsequent promotion of angiogenesis. *PDGFR-β* is significantly expressed in breast cancer cells[17,18]. Phosphorylated *PDGFR* regulates cell proliferation and migration *via PI3K-AKT*[19] and other signaling pathways, thereby participating in tumor angiogenesis (**Figure 1**). Wang et al. have reported that decreased levels of *PDGF-B* promote vascular normalization of breast cancer cells, increase cytotoxic drug delivery, and inhibit tumor growth[17]. In a mouse model of triple-negative breast cancer with lung metastasis formation, *PDGFR-β* blockade has been found to decrease cancer cell growth and migration, and consequently prevent lung metastasis[20]. Nevertheless, the specific mechanism of the *PDGF/PDGFRs* axis in the angiogenesis of breast cancer cells remains unclear. Further basic experiments are warranted to elucidate the relevant mechanisms.

Epidermal growth factor (EGF) and EGF receptor (EGFR)

EGF is a mediator with crucial roles in the proliferation, survival, differentiation, and migration of vascular endothelial cells, through *EGFR* binding. *EGFR* is activated by phosphorylation and is involved in regulation of tumor angiogenesis *via* its downstream signaling pathways (*MAPK*, *PI3K/AKT/PKB*, *STAT*, and *PLCγ/PKC*)[21] (**Figure 1**). *HER2*, a subtype of *EGFR*, is a frequent target in breast cancer treatment. *EGFR*-mediated downregulation of the *JAK-1/STAT-3* signaling pathway has been found to inhibit angiogenesis, significantly decrease the volume of breast cancer tissues, and inhibit tumor growth[21]. *EGFR* and *VEGFR* frequently share downstream signaling pathways. Furthermore, the expression of *EGFR* leads to an increase in *VEGFR* levels and consequently plays a crucial role in promoting angiogenesis[22]. Therefore, targeting *EGFR* to downregulate *VEGFR* expression is advantageous in cancer treatment. Nevertheless, many patients who undergo targeted *EGFR* therapy exhibit progression after 1 year[23]. Therefore, mechanisms underlying resistance and strategies to reverse resistance *via* targeted *EGFR* therapy must be further explored.

Other factors

Beyond the *VEGF/VEGFR*, *EGF/EGFR*, and *PDGF/PDGFR* axes, many other growth factors play indispensable roles in angiogenesis, such as fibroblast growth factor (*FGF*)/*FGFR4*, *hepatocyte growth factor* (*HGF*)/*c-Met*, *insulin-like growth factor* (*IGF*)/*IGFR*, and *transforming growth factor* (*TGF-β*) (**Figure 1**). Angiogenesis-related *FGFR4* is significantly upregulated in breast cancer, and promotes vascular endothelial cell proliferation and breast cancer angiogenesis *via* the *PI3K/AKT* signaling pathway[24]. *HGF* activates c-Met through phosphorylation of the tyrosine residues Y1234 and Y1235. Adaptor proteins bind several substrates, and downstream *MAPK* and *STAT* signaling pathways are consequently activated, thereby promoting angiogenesis in breast cancer[25]. Muoio et al. have reported that elevated *IGF* expression in patients with obesity and diabetes promotes breast cancer angiogenesis *via* the *S7A1/RAGE* downstream signaling pathway[26] (**Figure 1**). Notably, *TGF-β* increases angiogenesis in breast cancer by modulating endothelial–mesenchymal transition, potentially through *TGF-β*-induced expression of *Snail* and *Slug*[27]. Various growth factors play important roles in the angiogenesis of breast cancer. Therefore, anti-angiogenic therapies

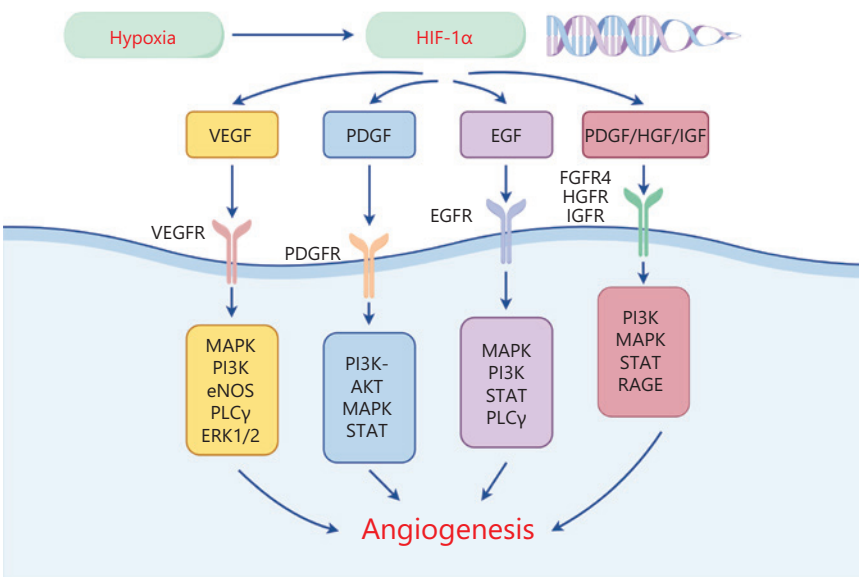

Figure 1 The hypoxia-inducible factor *HIF* promotes the transcription of angiogenesis-related factors. The *VEGF/VEGFR* signaling axis promotes angiogenesis *via MAPK*, *PI3K*, *PLCγ*, *ERK1/2*, and *eNOS*. The *PDGF/PDGFR* signaling axis promotes angiogenesis *via MAPK*, *PI3K-AKT*, and *STAT*. The *EGF/EGFR* signaling axis promotes angiogenesis *via MAPK*, *PI3K*, *PLCγ*, and *STAT*. Other signaling axes (*PDGF/HGF/IGF*) promote angiogenesis through *MAPK*, *PI3K*, *STAT*, and *RAGE*.

against these vascular factors can be beneficial. Further studies are warranted to validate the possibility of targeting single or multiple growth factors to increase the anti-angiogenic efficacy of breast cancer treatment.

Hypoxia-induced mechanisms

Oxygen is a crucial factor required for tumor growth, and the increasing oxygen demand during tumor development contributes to the formation of a hypoxic microenvironment. Under hypoxic conditions, tumors activate *HIF-1α*, which in turn stimulates tumor angiogenesis. Paradoxically, the resultant abnormal vasculature exacerbates hypoxic conditions and creates a vicious cycle, wherein the progressively abnormal TME continues to foster angiogenesis and hypoxia in tumors.

HIF-induced angiogenesis

Under hypoxia, the activity of *FIN-1* and *PHDs*, acting as oxidase-related groups, is inhibited, thus leading to decreased *HIF-1α* hydroxylation and proteasome degradation. Consequently, the cytoplasmic level of *HIF-1α* increases, and *HIF-1α* forms a heterodimer with *HIF-1β*. This heterodimer translocates to the nucleus, where *HIF-1* binds the activating protein *CREB* (*P300*) and the *hypoxia reactive element* (*HRE*), and subsequently initiates a series of hypoxia-induced cascades, including angiogenesis, through increased transcription of target genes, such as *VEGF*[28]. Recent studies have elucidated the role of *HIF-1* in breast cancer angiogenesis through the *SNHG1/miR-199a-3p/TFAM* axis[29]. Beyond *HIF-1*, the hypoxia-induced *HIF-2*-dependent pathway promotes angiogenesis in breast cancer by upregulating levels of the lncRNA RAB1B-AS231 through *HIF-2*. This event in turn increases the transcription of angiogenesis-related factor *VEGFA*. Knockdown of *HIF-2* has been shown to eliminate the increase in *RAB1B-AS231* expression, thereby decreasing angiogenesis in breast cancer[30] (**Figure 2C**). Given the current limitations of targeted *VEGF* treatment regimens, targeting *HIF*, a key regulator of

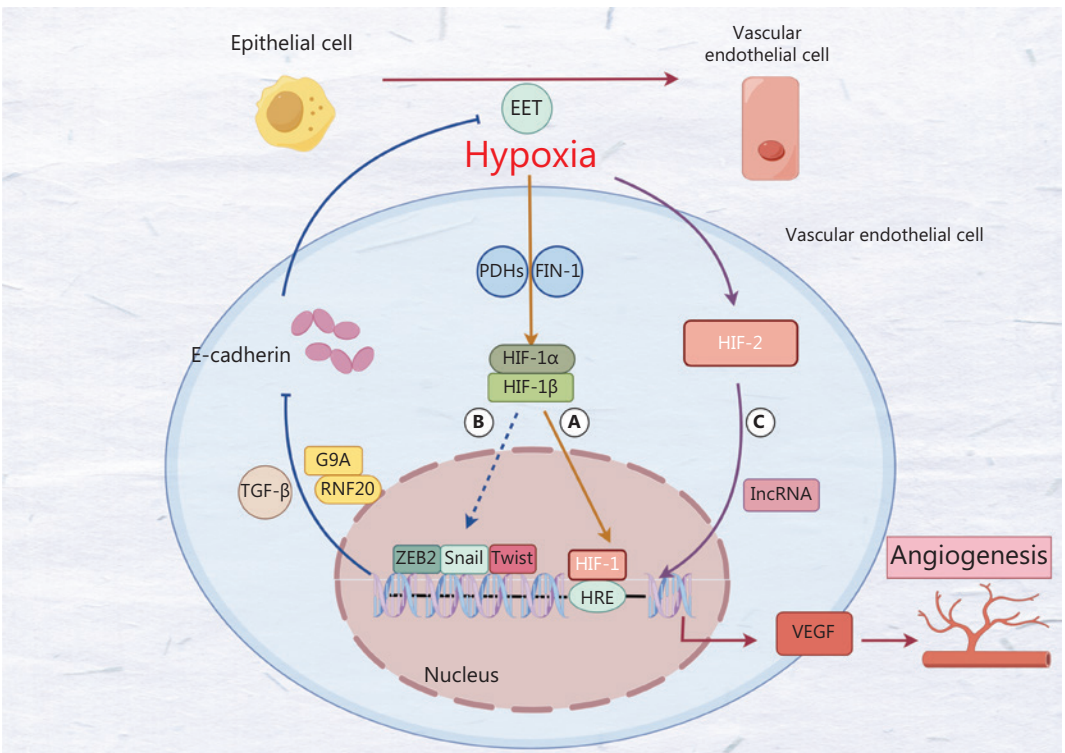

Figure 2 **A.** Hypoxia inhibits the activity of *FIH-1* and *PHD*, thereby promoting the expression of *HIF-1*. Subsequently, *HIF-1* stimulates the expression of VEGF, which in turn facilitates angiogenesis. **B.** *HIF-1* induces endothelial to mesenchymal transition by promoting the activity of the transcription factors Twist, Snail, and ZEB2, thereby stimulating angiogenesis. However, its specific mechanism is unclear. **C.** Hypoxia promotes *HIF-2* expression through a lncRNA that also promotes angiogenesis.

angiogenesis in breast cancer, may emerge as a promising new therapeutic approach.

Epithelial–endothelial transition (EET)

Epithelial–mesenchymal transition (EMT) is a prevalent phenomenon. Research has revealed that the same key factors are involved in both EET and EMT. Consequently, EET is generally considered a phenotype of EMT[31]. Under hypoxia, breast cancer cells show a decrease in tight junction proteins (such as E-cadherin and occludin) and an increase in vimentin and VE-cadherin. Tumor epithelial cell transition to endothelial cell phenotypes subsequently promotes the proliferation of tumor vascular endothelial cells and angiogenesis[32] (**Figure 2A**) Numerous EET-associated signaling pathways are directly or indirectly regulated by hypoxia. Transcription factors such as *Twist*, *Snail*, and *ZEB2*, which are directly regulated by hypoxia, play major roles in this process and share a frequent promoter: the *HRE*. Under hypoxia, binding of HIF to *HRE* promotes the transcription of *Twist*, *Snail*, and *ZEB2*[33-35] (**Figure 2B**). Twist proteins downregulate the expression of E-cadherin in breast cancer, thereby promoting EET. This process may be involved in EET progression *via* activation of *Wnt/β-catenin* signaling by the *JPX/miR-33a-5p/Twist1* axis[36]. However, this signaling pathway was discovered and validated by Pan et al. in the EET in lung cancer, and further research is warranted to confirm its presence in breast cancer[37]. The *Snail* gene has been found to interact with *RNF20* (*E120* ubiquitin-protein ligase with monoubiquitinated *H3BK2*) and *G9a* (methyltransferase of *H3K9me2*) in breast cancer, and to subsequently inhibit the expression of E-cadherin. The *Snail* gene also promotes tumor EET and induces tumor angiogenesis[38,39]. Consequently, hypoxia plays a crucial role in tumor angiogenesis, and reversing the tumor hypoxic microenvironment may aid in the treatment of anti-angiogenic and tumor vascular normalization.

Tumor angiogenesis and drug resistance

The abnormal new vasculature formed through tumor angiogenesis impedes oxygen delivery and increases the hypoxic microenvironment of breast tumors. This condition has been found to directly or indirectly induce drug resistance in breast cancer through various mechanisms[5]. The abnormal vasculature disrupts the delivery and distribution of drugs, thereby preventing effective drug concentrations from being achieved within tumors and leading to drug resistance. Tumor angiogenesis further alters the composition of immune cells in the microenvironment, by converting immune cells into tumor-related immunosuppressive cells, and promoting breast cancer progression and drug resistance[7,40].

Hypoxia-induced resistance

Immediate effects

Hypoxia directly induces the transcription of drug resistance-associated genes, namely *MDR1*, *MRP1*, and *BRCP*, which are members of the same ABC transporter family. The expression of ABC transporters increases under hypoxic conditions, thus facilitating drug efflux, decreasing effective drug concentrations, and fostering drug resistance in breast cancer. Expression of the multidrug resistance gene (*MDR1*) frequently contributes to drug resistance in various cancers. Che et al. have demonstrated that HIF-1α directly binds the *MDR1* promoter and promotes *MDR1* expression, as confirmed with ChIP assays[41]. In breast cancer cells, *AGR2* expression decreases the degradation of *HIF-1α* and increases *MDR1* transcription, thus decreasing epirubicin uptake and promoting doxorubicin (*DOX*) resistance in breast cancer cells[42]. *MDR1* is regulated through hypoxia-induced *Notch1* signaling and contributes to the development of tumor resistance[43]. Under hypoxic conditions, increased *HIF-1α* activity promotes the *BRCP* expression[41]. *DOX* has been found to induce the production of reactive oxygen species, thereby synergistically upregulating the expression of *MDR1* and *BRCP* in conjunction with the high activity of *HIF-1α* under hypoxia. This process limits the uptake of *DOX* and promotes the emergence of drug resistance[44].

Indirect effects

The hypoxia-induced acidic microenvironment of tumors can affect drug efficacy[45], and promote the phenotypic expression of breast cancer stem cells (CSCs) and the acquisition of *MDR* in breast cancer. In a hypoxic environment, *HIF-1α* is essential for promoting the expression of the target gene *VEGF*, which in turn stimulates angiogenesis, exacerbates hypoxia, and supports the development of drug resistance in breast cancer. Under hypoxia, enhanced anaerobic metabolism leads to the accumulation of acidic substances, such as lactic acid, and an increase in the microenvironment pH. The pH value of the TME is typically 10 to 30 times

higher than that of normal tissues[45]. The efficacy of *DOX* against breast cancer cells is limited by the low pH TME induced by hypoxia simulation. Simultaneously, the degree of pH decrease precisely corresponds to the extent of tumor growth delay[46]. Breast CSCs exhibit unlimited proliferation and diverse differentiation potential, and consequently promote tumor immune evasion. Cancer stem cells usually overexpress *ABC* transporters, which contribute to dysregulation of the signal transduction network and play essential roles in tumor *MDR*[47]. *HIF* is involved in the expression of CSC in breast cancer. Through FACS, Brooks et al. have observed that *HIF* is highly active under hypoxic conditions and promotes the transcription of the target gene *ITGA6*, which, in conjunction with other integrins, is enriched in breast stem cells and promotes the acquisition of *MDR* phenotypes in breast cancer[48]. HIF participates in the expression of *glutathione S-transferase omega 1* (*GSTO1*), thereby promoting endoplasmic reticulum release of Ca^{2+}; inducing the recruitment of CSC through the *PYK2* → *SRC* → *STAT3* signal transduction induced by cisplatin; and contributing to the occurrence of drug resistance in breast cancer[49] (**Figure 3A**). *HIF-1α* activity increases under hypoxia. *HIF-1α*, which promotes transcription under hypoxia, directly promotes the expression of cancer stem cell phenotypes in liver cancer. However, whether *HIF-1α* directly promotes the expression of breast cancer stem cell phenotypes has not been validated (**Figure 3B**). The *RAS/RAF/MEK/ERK* kinase cascade enhances the translation of *HIF-1α* by phosphorylating eukaryotic translation *initiation factor 4E* (*eIF-4E*). Furthermore, this kinase cascade enhances the transcriptional activity of *HIF-1α* by binding the *TAD* sequence of *HIF-1α* through the transcriptional co-activators p300/CBP (**Figure 3C**). In breast cancer cells, loss of the tumor suppressor gene *PTEN* is frequently observed. The loss of *PTEN* promotes activation of the *PI3K/AKT* pathway, and its downstream mTOR protein activates *eIF-4E* and consequently promotes the translation of *HIF-1α* protein[50,51] (**Figure 3D**). *HIF-1α* forms a heterodimer with *HIF-1β* in the cytoplasm, translocates into the nucleus, and binds specific *HREs* on DNA, where it acts as a transcription factor for the downstream target gene *VEGF* (**Figure 3E**). Subsequently, the proliferation of endothelial cells increases, angiogenesis in breast cancer is improved, and hypoxia is further exacerbated. Thus, the development of drug resistance in breast cancer occurs through various direct and indirect mechanisms.

Drug concentration, efficacy, and resistance

Drug concentration

The drugs used to treat tumors typically must reach effective concentrations within tumors to exert anti-tumor effects. Drug concentrations are affected by the abnormal and immature tumor vasculature system, as well as by the activation of drug efflux transporters under the hypoxic tumor environment[52].

MDR1, also known as permeability glycoprotein (*P-gp*), is a transmembrane transport protein that recognizes and controls drug efflux from tumor tissues and eventually promotes drug resistance in breast cancer by altering drug distribution in tumors[52]. *HIF-1α* is highly expressed after tumor angiogenesis, and subsequently binds *P-gp*, and upregulates *P-gp* gene expression. This upregulation then promotes drug efflux. Consequently, achieving effective drug concentrations in the tumor becomes difficult and ultimately leads to drug resistance in breast cancer. *HIF-1α* inhibition decreases *P-gp* levels in tumors and partially reverses *MDR* caused by *MDR1* (*P-gp*)[41]. A recent study has described the use of novel nanomolecular materials to directly downregulate *P-gp* gene expression and enhance the sensitivity of breast cancer cells to chemotherapy[52].

Drug efficacy

Antineoplastic drugs typically require certain conditions to exert optimal therapeutic effects. For example, compared to cells with an inactive cell cycle, chemotherapy drugs are usually more effective against active tumor cells. Tumor cells typically undergo active DNA replication, and chemotherapy drugs act on the cell cycle[53]. Abnormal tumor vascular systems often affect pH levels and create a hypoxic environment, which in turn affects the efficacy of antineoplastic drugs.

Tumor angiogenesis often results in a low-pH and hypoxic TME, which eventually limits drug efficacy. The low-pH TME has been reported to promote the resistance of breast cancer cells to *DOX*[46]. In addition, the hypoxic microenvironment caused by impaired oxygen delivery due to abnormal vascular systems affects drug efficacy. In breast cancer treatment, chemotherapeutic drugs, such as docetaxel, are among the most frequently used therapeutic agents. Typically, these drugs exert therapeutic effects by interfering with DNA synthesis, inducing apoptosis, and inhibiting cell division in breast cancer cells. Although chemotherapeutic drugs are more effective against actively proliferating cancer cells than proliferating

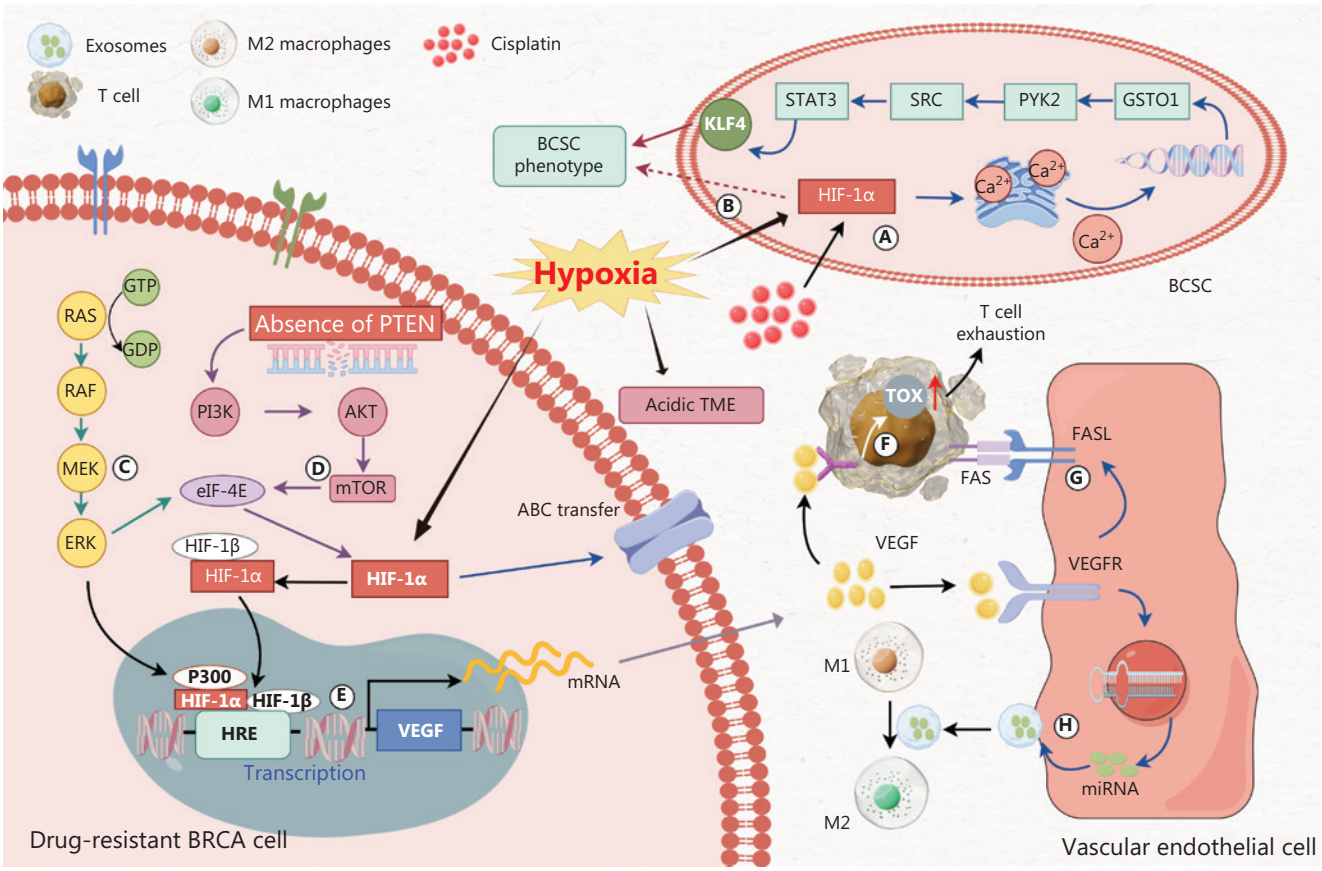

Figure 3 **A.** Cisplatin-induced *HIF-1α* facilitates the release of calcium ions from the endoplasmic reticulum. The released calcium ions in turn promote the expression of glutathione S-transferase omega 1 (GSTO1). GSTO1 induces the recruitment of cancer stem cells (CSCs) through the *PYK2* → *SRC* → *STAT3* signal transduction pathway. *STAT3* activity promotes the BCSC phenotype by upregulating the expression of the pluripotency factor *KLF4*. **B.** Hypoxia-induced *HIF-1α* directly promotes the cancer stem cell phenotype in liver cancer. However, whether *HIF-1α* directly promotes the breast cancer stem cell phenotype remains to be validated. **C.** The *RAS/RAF/MEK/ERK* kinase cascade enhances the translation of *HIF-1α* by phosphorylating the eukaryotic translation *initiation factor 4E* (*eIF-4E*). Furthermore, this cascade pathway facilitates the interaction between transcriptional co-activators *p300/CBP* and *HIF-1α*, thereby augmenting the binding capacity of HIF-1α to *HRE*. **D.** Loss of *PTEN* promotes activation of the *PI3K/AKT/mTOR* pathway, thereby activating *eIF-4E*, which in turn promotes *HIF-1α* translation. **E.** *HIF-1α* forms a heterodimer with *HIF-1β* in the cytoplasm, translocates into the nucleus, and acts as a transcription factor binding specific *HREs* on DNA, thus promoting transcription of the downstream target gene *VEGF*. **F.** *VEGF* binding to *VEGFR* on the surfaces of T cells promotes *TOX* expression and leads to T cell exhaustion. **G.** *VEGF* binds *VEGFR* and promotes the expression of *FASL* ligands in epithelial cells, thereby facilitating T cell apoptosis. **H.** *VEGF/VEGFR* signaling promotes the transcription of miRNAs (*miR-142-5p*, *miR-183-5p*, and *miR-222-3p*) and facilitates their extracellular transport *via* exosomes, thereby promoting the polarization of M2 macrophages.

inactive cancer cells, decreased aerobic oxidation in cancer cells under hypoxia decreases cell activity and proliferation, and consequently limits the effectiveness of chemotherapeutic drugs[53]. However, no specific measures are currently available to prevent or treat drug resistance caused by angiogenesis in breast cancer. Therefore, investigating the mechanisms of action of various drugs and devising strategies to prevent drug resistance will be imperative to achieve more precise and effective targeting of breast cancer cells.

Tumor immunity and resistance

The formation of abnormal vascular systems due to tumor angiogenesis leads to decreased blood perfusion, which in turn hinders the immune cell infiltration that effectively kills tumor cells. Tumor angiogenesis is associated with intrinsic mechanisms such as the *MAPK/PI3K* and *WNT/β-catenin* pathways, which contribute to drug resistance development[54]. In contrast, angiogenic factors promote changes in extracellular

factors and contribute to immunosuppressive TME formation, such as peripheral dendritic cell (DC) maturation, inhibition of T-cell activation, and polarization of macrophages toward the M2-like tumor-associated phenotype[55]. Angiogenesis induces an immunosuppressive TME that promotes the resistance of breast cancer to immunotherapeutic drugs[56].

Tumor-associated internal resistance

The oncogenic signaling of the *MAPK* pathway associated with breast cancer is linked to the *c-myc* pathway through the *VEGF* promoter, which promotes *VEGF* transcription; subsequently, secreted proteins inhibit the recruitment and infiltration of specific T-cells in tumors[57]. In addition, the loss of *PTEN*, a tumor suppressor gene, plays a major role in the invasion and progression of breast cancer. *PTEN* loss and *VEGF* overexpression are closely correlated in breast cancer. *PTEN* loss promotes *VEGF* expression by inducing *HIF-1α* and activating the *PI3K-AKT* pathway[58,59]. *PTEN* loss in breast cancer is associated with resistance to chemotherapy[58] and immune checkpoint-associated immunotherapy, which may be associated with the activation of the *PI3K-AKT* pathway, thereby affecting T-cell infiltration in tumors[60]. Both miR526b and miR655 regulate *PTEN* expression and upregulate *VEGF* expression, and hence promote angiogenesis in breast cancer. Altered *PTEN* pathway expression has been found to enhance the efficacy of anti-PD-1 and anti-CTLA-4 antibodies in mouse models[60] and to improve the chemoresistance of breast cancer cells to *DOX*[61]. Moreover, miR526b and miR655 may serve as targets for improving drug resistance in breast cancer *via* the *PTEN/PI3K* pathway. The *WNT* pathway, which is often involved in tumorigenesis signaling, is crucial for tumor angiogenesis. This pathway, under stabilization by β-catenin, is closely associated with immune suppression in tumors[62]. Moreover, this pathway has been associated with increased β-catenin levels, and decreased DC chemokine CCL103 and mature CD4 DC levels in tumors. The *Wnt/β-catenin* pathway, targeting suppresses stemness and angiogenesis, improves *MDR* in breast cancer[62]. Compared with mice with *Wnt/β-catenin* pathway activation, mice lacking β-catenin exhibit markedly enhanced immunotherapeutic efficacy[54]. Conventionally, breast cancer has not been considered an immunogenic tumor. However, several recent studies have shown that breast cancer cells express immune inhibitory ligands, such as PD-1, which suppress CD8 T-cell activity and lead to immune resistance in breast cancer[63]. In addition, tumor-associated intrinsic pathways such as *MAPK/PI3K*, *WNT/β-catenin*, and PD-1 are closely associated with tumor angiogenesis, and interactions among these pathways affect DC maturation, and T-cell recruitment and activation, and subsequently promote drug resistance in breast cancer. Targeting the key factor *VEGFR2* promotes tumor vascular normalization, thus increasing immune cell infiltration and activation. Furthermore, low-dose anti-angiogenic therapy promotes *osteopontin* (*OPN*) secretion by $CD8^+$ T-cells. Subsequently, *OPN* induces tumor cells to produce *TGF-β*, which in turn upregulates PD-1 expression on immune cells and ultimately increases the sensitivity of breast cancer to PD-1 immunotherapy. The combination of anti-angiogenic therapy and anti-PD-1 immunotherapy has been found to effectively overcome drug resistance in breast cancer[64].

Tumor-associated external resistance

Beyond abnormal vascularization due to tumor angiogenesis, hypoxia, and low pH induce an immunosuppressive TME[65]. *VEGF* highly expressed on the endothelium of peripheral tumor blood vessels binds *VEGFR1*, and subsequently inhibits DC maturation and antigen presentation, and impedes T-cell activation and infiltration[66]. High *VEGF* expression promotes the accumulation of peripheral myeloid-derived suppressor cells (MDSCs), which are closely associated with cancer angiogenesis and immunosuppression[67]. MDSCs regulate breast CSCs *via* the *CXCL2-CXCR2* pathway, thereby inducing resistance to docetaxel[68]. Furthermore, MDSC targeting and inhibition *via* the *SDF1α/CXCR4* axis enhance the anti-tumor activity of chimeric antigen receptor (CAR)-T-cell immunotherapy in breast cancer[69]. High *VEGF* expression during angiogenesis in breast cancer decreases CD8 T-cell levels *via* the *HMG-bOX* (*TOX*) pathway, thereby increasing tumor-cell tolerance to immunotherapy[70] (**Figure 3F**). The combination of *VEGF*, *interleukin-10*, and *prostagl*an*din E2* promotes the expression of the death ligand *FasL* in endothelial cells. *FasL* is an ectopic expression product in mouse solid tumors and is undetectable in normal vascular systems. *FasL* promotes the tumor-specific exclusion of cytotoxic T-cells, facilitates the formation of an immunosuppressive TME, and leads to the development of drug resistance[71] (**Figure 3G**). In addition, *angiopoietin 2* and *placental growth factor*, which are associated with tumor angiogenesis, induce macrophage polarization toward the M2 phenotype, thereby leading to the development of an immunosuppressive TME[72]. Moreover, vascular endothelial cells in the breast cancer microenvironment release several miRNAs (*miR-142-5p*, *miR-183-5p*, and *miR-222-3p*) that are transported through

extracellular vesicles, and subsequently regulate macrophage remodeling and promote macrophage polarization toward the M2 phenotype[73] (**Figure 3H**). Anti-angiogenesis treatment to promote tumor vessel normalization has been found to reverse the tumor immunosuppressive microenvironment and improve cancer treatment efficacy[74]. Thus, the combination of anti-angiogenesis therapy and immunotherapy may enhance the efficacy of immunotherapy against breast cancer. However, several challenges exist in the application of such combination treatment strategies. Future studies should focus on the appropriate dosages of anti-angiogenic drugs and their potential toxicity after combined treatment, to overcome persisting challenges.

Drugs to reverse drug resistance in breast cancer

Breast cancer treatments include primarily chemotherapy, targeted therapy, and immunotherapy. Because angiogenesis plays a crucial role in the development of drug resistance in breast cancer, anti-angiogenic therapy has been found to improve the TME and drug perfusion, thereby partially reversing drug resistance. Studies to date have investigated various anti-angiogenesis methods, including the use of nanoparticle drugs, to promote tumor vessel normalization and reverse drug resistance[75].

Reversal of chemotherapy drug resistance

Eribulin mesylate, a synthetic analog of halichondrin B, directly inhibits cancer cells by binding microtubule proteins. This analog has been widely applied in locally advanced or metastatic breast cancer. However, eribulin directly acts on angiogenesis-associated pathways, including *VEGF* (*Vegfa*, *Vegfr1*, *Vegfr2*, and *Vegfr3*), *Notch* (*Dll4*, *Jag1*, and *Notch4*), *Eph* (*Efnb2*, *Epha2*, and *EphB1*), and *WNT* (*Wnt5a*, *Wnt11*, and *BPM4*), thus resulting in vascular remodeling. Increased vascular perfusion and enhanced drug delivery after eribulin treatment markedly increase capecitabine's efficacy, thereby preventing resistance of breast cancer cells to capecitabine[76] (**Table 1**). Gambogic acid (GA), a naturally occurring dry resin found in *Garcinia hanburyi*, selectively targets the *HIF-1α/VEGF* pathway and inhibits tumor angiogenesis[77]. Furthermore, GA inhibits *P-gp* gene expression, thereby preventing drug efflux. GA alters drug distribution, increases perfusion, enhances intratumoral drug concentration, and reverses resistance to *DOX* in drug-resistant breast cancer cells *via* the combined action of these 2 mechanisms, and ultimately increases sensitivity to the drug[78] (**Table 1**). Recently, novel nanomedicines have been investigated to provide additional avenues for reversing drug resistance in breast cancer by promoting tumor vascular normalization *via* anti-angiogenesis. The nanodrug AuNP-Qu-5 synthesized from quercetin (Qu) and gold nanoparticles (AuNPs), enhances tumor vascular normalization by downregulating

Table 1 Drugs for reversing drug resistance

Drugs	Targets	Effect/mechanism
Reversal of chemotherapy drug resistance		
Eribulin	*VEGF*, *Notch*, *Eph*, and *WNT*	Eribulin increases the efficacy of capecitabine
Gambogic acid (GA)	*HIF-1α*, *VEGF*, and *P-gp*	GA enhances intratumoral doxorubicin concentration
Au NPs-Qu-5	*VEGFR2*	Au NPs-Qu-5 increases drug penetration
LMWH and QU	*Bfgf*, *VEGF*, *P-gp*, *MRP1*, and *BCRP*	LMWH and QU inhibit drug efflux
Reversal of targeted drug resistance		
Nintedanib	*VEGFR*, *PDGF*, *FGFR*, *FLT3*, and *SRC* family	Nintedanib increases the efficacy of single-target *VEGF* drugs
Matrine	*HIF*, *BRCA CSC*	Matrine inhibits resistance of breast cancer to anti-angiogenic therapy
Lapatinib	*EGFR/HER-2*	Lapatinib reverses resistance to trastuzumab
Gold nanoparticles and pulsed femtosecond lasers	*HER-2*	Gold nanoparticles with anti-*HER2* antibody functionality reverse resistance to trastuzumab

VEGFR2 expression, improving blood flow, and increasing drug penetration[79] (**Table 1**). A nanodrug comprising low-molecular-weight heparin and QU has been reported to target basic fibroblast growth factor and *VEGF*, inhibit drug efflux protein expression (*P-gp*, *MRP1*, and *BCRP*), and prevent drug resistance in breast cancer[80] (**Table 1**). Xihuang pills act on *PI3K/Akt/mTOR* signaling, a key pathway in blood vessel formation, thus providing a possibility for reversing resistance to chemotherapy[81]. In addition, preliminary studies have elucidated the mechanism of reversing resistance to paclitaxel in breast cancer *via* anti-angiogenesis. CircBACH217 reverses the resistance of breast cancer to paclitaxel by inhibiting *G1BP7* expression[82]. However, basic experiments remain necessary to verify the feasibility of nanodrug therapies.

Reversal of targeted drug resistance

Targeted therapies such as *VEGF* inhibitor treatment, have faced challenges in achieving ideal therapeutic effects in breast cancer treatment[83]. Nintedanib, a multi-target receptor tyrosine kinase inhibitor, targets *VEGFR*, *PDGF*, *FGFR*, *FMS-associated tyrosine kinase 3*, and *SRC* family kinases, thus increasing the efficacy of single-target *VEGF* drugs[84] (**Table 1**). Matrine and bortezomib selectively target and inhibit *HIF*, alleviate the hypoxic environment, and prevent hypoxia-induced resistance to anti-angiogenic therapy in breast cancer. The matrine and trastuzumab combination targets breast CSCs and alleviates the resistance of breast cancer cells to anti-angiogenic therapy[85] (**Table 1**). High *FGF2* expression in breast cancer cells promotes resistance to targeted *VEGF* and *PDGF* drugs *via* a *PDGFRβ*-dependent mechanism. Moreover, combination therapy targeting *VEGF* and *PDGF* reverses the resistance of high *FGF2*-expressing breast cancer cells to single-targeted drugs[14]. Nevertheless, patients with *HER*-2-positive breast cancer can develop resistance to targeted *HER-2* therapy, such as trastuzumab, after several years[86]. A phase III clinical trial examining lapatinib, a dual *EGFR/HER-2* tyrosine kinase inhibitor that inhibits the *EGFR/HER-2* signaling pathway, has shown that lapatinib reverses resistance to trastuzumab in patients with breast cancer with trastuzumab resistance[86] (**Table 1**). In addition, Nunes et al. have developed AuNPs with anti-*HER2* antibody functionality, used in combination with pulsed femtosecond lasers, to reverse the resistance of breast cancer cells to trastuzumab. The combination of the AuNPs and photothermal therapy markedly decreases microvascular density in the tumor area, thereby inhibiting the growth of trastuzumab-resistant breast cancer cells *via* anti-angiogenesis, and ultimately reversing resistance to trastuzumab[87] (**Table 1**).

Reversal of immunotherapy drug resistance

Immunotherapy has emerged as a treatment method in recent years. Antibody-drug conjugates (ADCs) have been found to be effective in combined immunotherapy and targeted therapy. This class of drugs is formed by linking a specific antibody to a toxic payload and works by binding target antigens on the surfaces of breast cancer cells through their specific antibodies. After the drugs enter the cells through endocytosis, the toxic payload is released inside the cells through the action of lysosomes and subsequently exerts cell-killing effects[88]. The combination of specific antibodies and targeted toxins partially reverses resistance to conventional targeted drugs[89]. In the EMILIA trial (NCT00829166), ADC class drugs, compared with lapatinib plus capecitabine, in populations with low HER-2 expression extended the progression-free survival by more than 3 months and the overall survival by 4 months. However, patients with breast cancer exposed to ADC therapy continue to develop resistance after a certain period of time, primarily because ADC drugs can maintain progression-free survival in patients with advanced breast cancer patients for only several months to several years. Breast cancer cells acquire resistance through pathways such as downregulation of HER-2 expression and upregulation of ABC transporter protein expression[90]. Currently, many strategies are being explored to reverse drug resistance to ADC drugs. For example, the newly developed drug DS-8201a has higher membrane penetration and a greater drug payload than the traditional ADC drug T-DM1[91]. Moreover, anti-angiogenic therapy can increase the effective concentrations of ADC drugs within tumors by inhibiting the expression of ABC transport proteins. However, the dose toxicity effects of ADC drugs, such as lung injury, remain challenges that must be addressed.

Conclusions

Tumor angiogenesis, a major pathological process in breast cancer, is induced by a hypoxic TME and various angiogenic factors. An abnormal tumor vascular system further exacerbates tumor hypoxia and an immunosuppressive TME,

affects drug distribution, and promotes drug resistance in breast cancer. Drug resistance is a major cause of poor prognosis in many patients with breast cancer. The diverse mechanisms of angiogenesis in tumor treatment act as a double-edged sword by providing various therapeutic targets for targeting angiogenesis but also enabling tumors to escape from the action of single-target drugs, such as *VEGF*. This escape may be attributable to the activation of alternative growth factor-associated signaling pathways through diverse mechanisms, thus leading to continual promotion of tumor angiogenesis. Nevertheless, inhibiting tumor angiogenesis and promoting tumor vascular normalization are potential new mechanisms for reversing drug resistance in breast cancer. Anti-angiogenic approaches have improved the efficacy of chemotherapy and targeted therapy for breast cancer. Immunotherapy is a newly emerging treatment modality against breast cancer; however, the specific mechanism underlying the resistance of breast cancer cells to immune drugs remains unclear. Nevertheless, anti-angiogenic therapy has been demonstrated to increase the efficacy of immune drugs in tumor treatment[92].

This review provided an overview of the correlation between tumor angiogenesis and drug resistance development in breast cancer, as well as methods for reversing drug resistance *via* anti-angiogenic therapy. However, challenges persist in applying these approaches in clinical practice. First, determining the appropriate dosage of anti-angiogenic drugs to increase the efficacy of drug-resistant treatments against breast cancer is difficult. In addition, whether combination therapy might increase drug toxicity remains uncertain. Hence, more preclinical studies must be performed to validate the rationale and safety of combination therapy[74]. Anti-angiogenic therapy often has a reversible and transient vascular normalization window, depending on the drug type and dosage. Thus, future studies focusing on reversing drug resistance in breast cancer *via* anti-angiogenic therapy should examine the use of specific anti-angiogenic drugs and their methods of administration[93]. Moreover, different breast cancer cell lines may exhibit varying sensitivity to anti-angiogenic therapy. To further investigate tumor angiogenesis markers for breast cancer for evaluation of anti-angiogenic therapy efficacy, promoting vascular normalization may be a necessary prerequisite for reversing drug resistance. Finally, this review summarized the potential mechanisms of resistance to anti-angiogenic therapy in reversing drug resistance in breast cancer immunotherapy. For instance, targeting the *SDF1α/CXCR4* axis enhances the efficacy of CAR-T cell immunotherapy. Specific drugs targeting drug resistance reversal *via* anti-angiogenic therapy in breast cancer immunotherapy are under development[69].

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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