

# Acquired tumor resistance to antiangiogenic therapy: Mechanisms at a glance

Bahare Zarrin, Farzane Zarifi<sup>1</sup>, Golnaz Vaseghi<sup>2</sup>, Shaghayegh Haghjooy Javanmard

Department of Physiology, Applied Physiology Research Center, Isfahan University of Medical Sciences, <sup>1</sup>Department of Pharmacology, Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, <sup>2</sup>Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Angiogenesis is critical for oxygen and nutrient delivery to proliferating tumor cells. Therefore, as angiogenesis is required and vital for the tumor growth and metastasis. Antiangiogenic therapy is considered to be beneficial for tumor growth prevention due to starvation of tumor of oxygen and nutrients, but in some cases, the benefits are not permanent. Tyrosine kinase inhibitors and many other agents often target angiogenesis through inhibition of the vascular endothelial growth factor (VEGF) pathway. Although preclinical studies showed satisfactory outcomes in tumor growth inhibition, antiangiogenic therapy in the clinical setting may not be effective. The resistance observed in several tumor types through alternative angiogenic "escape" pathways contributes to restoration of tumor growth and may induce progression, enhancement of invasion, and metastasis. Therefore, activation of major compensatory angiogenic pathways, sustaining tumor angiogenesis during VEGF blockade contributing to the recurrence of tumor growth overcome antiangiogenic strategies. In this review, we summarize the novel mechanisms involved in evasive resistance to antiangiogenic therapies and represent different cancer types which have the ability to adapt to VEGF inhibition achieving resistance to antiangiogenic therapy through these adaptive mechanisms.

**Key words:** Angiogenesis inhibitors, antiangiogenic resistance, metastasis, tumor growth restoration

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## INTRODUCTION

Cancer, a disease involving abnormal cell growth, has a potential to invade and spread to other parts of the body. There are no symptoms at initial stage. Some general symptoms including unintentional weight loss, fever, excessive fatigue, and some changes to the skin appear as the mass grows.

In 2012, 14.1 million new cases and 8.2 million deaths were projected to occur in 20 large "areas" of the world. Estimates of the worldwide incidence and mortality from several major cancers showed that the most commonly diagnosed cancers were lung (1.82 million), breast (1.67 million), and colorectal (1.36 million); the most common causes of cancer death were lung

cancer (1.6 million deaths), liver cancer (745,000 deaths), and stomach cancer (723,000 deaths).<sup>[1]</sup>

Angiogenesis is critical for tumor growth and metastasis. Proliferating tumor cells activate angiogenesis to provide oxygen and nutrients for tumor cells.<sup>[2]</sup> Induction of angiogenesis obliges the balance of angiogenesis inducers and inhibitors toward a pro-angiogenic environment.

The less angiogenesis, the less tumor growth is observed. In 1972, Folkman hypothesized that by hindering blood supply, tumor could be starved into remission and suggested antiangiogenesis as a new anticancer strategy for the first time.<sup>[3]</sup> Until 2005, Folkman's laboratory discovered 12 angiogenesis inhibitors (AIs). AIs characterization as well as the isolation and cloning of vascular endothelial growth factor A (VEGFA) was a breakthrough in understanding of

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**Address for correspondence:** Dr. Shaghayegh Haghjooy Javanmard, Department of Physiology, Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: [shaghayeghhaghjoo@yahoo.com](mailto:shaghayeghhaghjoo@yahoo.com)

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the mechanism of angiogenesis. Understanding the function of VEGFs and their receptors in angiogenesis led to the US Food and Drug Administration approval of bevacizumab (BVZ) (a monoclonal antibody for VEGFA) as the first antiangiogenic drug for colorectal cancer in 2004.<sup>[4]</sup> Consequently, many AIs were developed including monoclonal antibodies, angiogenesis peptide inhibitors, to small molecule drugs and microRNAs.<sup>[5]</sup>

Drug development is limited due to therapeutic resistance. Overall survival does not lengthen for a long time and there is no permanent cure for renal cancer cells (RCCs), breast and colon cancers.<sup>[6-8]</sup>

Adaptation of angiogenic tumors to antiangiogenic drugs through acquiring different means evading the treatment is a controversial hypothesis in many studies.<sup>[9]</sup>

Among evasive resistance, many alternative pathways are activated to assure tumor growth whereas the antiangiogenic target remains inhibited.<sup>[10]</sup>

The crucial mechanisms of evasive resistance consist of revascularization, tumor vasculature protection, accentuated invasiveness of tumor cells, and increased metastatic manner.

In this review, we elaborate the potential mechanisms of the transitory efficacy of the current AIs that summarized in Table 1, based on-clinical and preclinical investigations.

## SOME MECHANISMS OF ANTIANGIOGENIC RESISTANCE

### Upregulation of alternative angiogenic factors

Tumor vasculature blockade by angiogenic inhibitors leads to the release of many proangiogenic factors and cytokines such as placental growth factor (PGF), VEGF, Angiopoietin 1 (ANG1), and fibroblast growth factor (FGFs), granulocyte colony-stimulating factor (G-CSF) and stromal cell-derived factor 1 (SDF1).<sup>[11]</sup>

The circulating levels of FGF-1 and -2, angiopoietin-1, ephrin-A1 and A2 increased pancreatic tumors after anti-VEGF treatment. Upregulated Ephrin-A2 is observed in malignant tumors.<sup>[12]</sup>

Vascular endothelial growth factor receptor (VEGFR) blockade upregulates FGF-2, SDF-1, and circulating endothelial cells (ECs) in glioblastomamultiforme patients.<sup>[13]</sup>

In addition, increased levels of PIGF and VEGF have been observed in colorectal, and renal cancer patients received tyrosine kinase inhibitors.<sup>[14]</sup>

Edoglin (CD105), a transforming growth factor (TGF)- $\beta$  coreceptor, has been shown to be highly expressed after anti-VEGF therapy in a pancreatic cancer model.<sup>[15]</sup> TGF- $\beta$ /ALK1 signaling is facilitated due to upregulation of endoglin expression during tumor angiogenesis.<sup>[16]</sup>

### Recruitment of vascular progenitor cells

The release of proangiogenic factors (PLGF, VEGF, ANG1, and FGFs) resulted from vascularization blockade leads to the recruitment of various bone marrow-derived cells (BMDCs) to elicit new blood vessels nourishing tumors. Proangiogenic BMDCs consist of stem cells involving in blood vessels production and vascular modulatory cells infiltrating into tumor stroma. ECs and pericytes compromised from their progenitors form blood vessels which are protected by pericyte envelop.<sup>[17]</sup> Vascular modulators include proangiogenic monocytes, such as tumour-associated macrophages (TAMs), and immature monocytic cells including TIE2<sup>+</sup> monocytes, VEGFR1<sup>+</sup> hemangiocytes, and CD11b<sup>+</sup> myeloid cells.

Endothelial to mesenchymal transition depending on tumor characteristics leads to more angiogenic and invasive capacities.<sup>[18]</sup>

Antiangiogenic therapy induced hypoxia activates hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) in tumor cells contributing to SDF1, and VEGF secretion may promote movement and assemblage of endothelial progenitor cells (EPCs). Differentiated ECs from their progenitors (EPC) under VEGF and SDF1 chemotactic factors secretion, incorporate into newly forming blood vessels.<sup>[19]</sup>

SDF1 stimulates CXCR7 leading to proangiogenic cytokines secretions by EPCs to angiogenesis promotion. In multiple myeloma, CXCR7-SDF1 signaling is involved in migration and homing of angiogenic immune cells into areas of tumor growth.<sup>[20]</sup>

### Immunologic factors infiltration and antiangiogenic resistance

Hypoxic conditions due to antiangiogenic therapy result in recruitment and expansion of myeloid derived suppressor cells (MDSCs), leading to a weakened antitumor response. MDSCs represent promising targets for therapy by regulation of T-cell exclusion through a variety of mechanisms. Neutrophils, T helper cells, and macrophages play important roles in resistance to antiangiogenic therapy. G-CSF expression stimulated by tumor infiltrating T helper type 17 cells and interleukin-17 (IL-17), results in recruitment of MDSC into the tumor tissue and tumor angiogenesis.<sup>[21]</sup> This is why Th17 cell function inhibition makes tumors sensitive to anti-VEGF therapies.<sup>[22]</sup>

**Table 1: Some mechanisms of acquired resistance to antiangiogenic therapy**

Study	Type of inhibitor	Type of cancer	Mechanism	Compensatory pathway	References
Motzer and Bukowski, 2006 Batchelor <i>et al.</i> , 2007 Falcon <i>et al.</i> , 2016	TKI VEGFR blockade	Colorectal and renal cancer Glioblastomamultiforme	Upregulation of proangiogenic factor depending on cancer type	Neovascularization	[14] [13] [11]
Azab <i>et al.</i> , 2014	CXCR7 inhibitor	Multiple myeloma	Recruitment of vascular progenitor cells, increased angiogenic signaling	CXCR7-SDF 1 signaling	[20]
Guo <i>et al.</i> , 2013	Tyrosine kinase inhibitor	Malignant hepatoma	Immunologic factors infiltration	Increased CSF 1, SDF 1 $\alpha$ and VEGF for inviting macrophages	[25]
Pinto <i>et al.</i> , 2016	VEGFR inhibitor	Ovarian and esophageal cancer xenografts	Increased pericyte coverage	Endothelial cell protection against antiangiogenic therapy	[32]
Leenders <i>et al.</i> , 2004 Frentzas <i>et al.</i> , 2016	Anti VEGF	Cerebral melanoma, gliomas, liver metastasis	Vessel co-option	Growth of cells along the existing vasculature	[34] [33]
Hillen and Griffioen, 2007 Kuczynski <i>et al.</i> , 2016	-	Malignant melanoma, sarcoma, glioma, breast cancer, and many other cancer types	Vessel mimicry	Formation of vascular-like structures in the absence of endothelial cells	[37] [36]
Grepin <i>et al.</i> , 2012 Pàez-Ribes <i>et al.</i> , 2009	Thyrosin kinase inhibitor VEGF inhibition	RCC Mouse models of glioblastoma and pancreatic neuroendocrine carcinoma	Increased invasive and metastatic manner	decreased integrity of the tumor Upregulation of some EMT-related genes	[47] [48]
Hu <i>et al.</i> , 2012 Prieto-Domínguez <i>et al.</i> , 2016	Bevacizumab	Glioblastoma HCC	Autophagy	Maintaining energy production Activation of AMPK and HIF-1 $\alpha$ pathways provides tumor cells survival and treatment resistance	[49] [50]
Giuliano S <i>et al.</i> , 2015	Sunitinib	Renal cell cancer	Lysosomal sequestration	Prevent access of the drug, participating in the loss of efficacy of the drug	[54]
Naumov GN <i>et al.</i> , 2003 Schroeder, 2016	Doxorubicin treatment	Breast cancer and colon cancer cells	Dormancy	Cancer cells growth arrestment	[58] [55]
Croci <i>et al.</i> , 2014	Anti-VEGF mAB	B16-F0- and CT26-sensitive tumors implanted into syngeneic mice	Glycosylation-Dependent Resistance	Activation of VEGFR2 signaling	[60]

TKI = Tyrosine kinase inhibitor; VEGF = Vascular endothelial growth factor; VEGFR = Vascular endothelial growth factor receptor; CSF = Colony-stimulating factor; SDF = Stromal cell-derived factor; RCC = Renal cancer cell; EMT = Epithelial mesenchymal transition; HCC = Hepatocellular carcinoma; HIF = Hypoxia inducible factor

Increased recruitment of neutrophils during anti-VEGF therapy promotes tumor progression and treatment resistance. Tumor progression with mesenchymal characteristics is partly mediated by increased neutrophil infiltration through the expression of S100A4.

Therefore, targeting granulocytes and S100A4 may be beneficial in inhibiting the tumor malignant phenotype and diminishing antiangiogenic therapy resistance.<sup>[23]</sup>

Macrophages performing the role “bridging cells” between the cells are contributed in vascular

sprouting and therefore antiangiogenic resistance. A proinflammatory response induced by highly expressed IL-8 in VEGF-therapy resistant tumors can promote angiogenesis by recruiting proangiogenic CD11b<sup>+</sup> myeloid cells.<sup>[24]</sup>

According to a study by Guo *et al.*, it has been shown that there are increased CSF-1, SDF-1 $\alpha$ , and VEGF which are intrinsic chemokines for inviting macrophages<sup>[25]</sup> in malignant hepatoma treated with sorafenib (a tyrosine kinase inhibitor). In other word, TAMs have crucial roles in tumor angiogenesis in hepatocellular carcinoma tumors.

Bone marrow-derived TAMs are fundamental factors contributing to resistance to anti-VEGF therapy.<sup>[26]</sup>

### Increased pericyte coverage

The tumor vessels which are heavily covered by pericytes have been shown a decreased sensitivity for AIs.<sup>[27]</sup> Increased pericyte coverage promotes EC survival after antiangiogenic treatment.<sup>[28]</sup> Reduction in tumor vascularity after anti-VEGF therapy is also accompanied by distinctive functional slim and tightly pericyte covered vessels protecting ECs from anti-VEGF therapy.<sup>[29]</sup> Pericytes mediate neovessel maturation and protect ECs from antiangiogenic therapy.<sup>[30]</sup>

Increased number of vessels covered with pericytes has been observed in a preclinical malignant glioma model treated with temozolomide (a chemotherapy drug) and sunitinib.<sup>[31]</sup>

Moreover, Ovarian and esophageal cancer xenografts treated with BVZ were accompanied with increased pericyte coverage around vessels contributing to EC maintenance and resistance to VEGFR inhibitors.<sup>[32]</sup>

### Vessel co-option

A different strategy providing oxygen and nutrients for efficient tumor outgrowth is termed vessel co-option in which tumor cells give rise along the existing vasculature. No angiogenic growth factor is required for this process, and it has been observed after anti-VEGF treatment.<sup>[33]</sup>

Vessel co-option leads to sustained cerebral melanoma metastasis growth.<sup>[34]</sup> In fact, vessel co-option has been observed in several tumors such as gliomas and lung cancer.<sup>[35]</sup>

In addition, BVZ-treated patients with colorectal cancer liver metastases demonstrated a poor response to antiangiogenic therapy due to vessel co-option.

Moreover, vessel co-option has been reported in human breast cancer liver metastases, liver metastases nonsmall cell lung cancer, and lung metastases.<sup>[36]</sup>

In liver metastases, cancer cell motility mediated by the actin-related protein 2/3 complex is required for vessel co-option.

### Vasculogenic mimicry

Whereas vasculogenesis is the process of blood vessel formation through a *de novo* production of ECs, angiogenesis is the formation of new blood vessels from preexisting ones. The formation of vascular-like structures providing tumors oxygen and nutrients under the process of vasculogenic mimicry has been described in different tumor types such as malignant melanoma, sarcoma, glioma, breast cancer,

and many other cancer types.<sup>[37,38,39]</sup> Vasculogenic mimicry is deeply associated with poor patient survival.

Dedifferentiation of melanoma cells to form vasculature is a plausible mechanism induced by an ischemic microenvironment.<sup>[40]</sup>

According to the evidence from preclinical studies, antiangiogenic treatment with BVZ leads to increased vasculogenic mimicry.<sup>[41]</sup> The ability of cancer cells to form vasculature in the absence of ECs and anastomoses of these pseudovasculature with existing vasculature are crucial adaptation manners nourishing the tumor. Among the vasculogenic mimicry process, tumor cells are required to differentiate and gain ECs features such as expressing the endothelial markers VE-cadherin, TIE1, ephrin A2. Mosaic vessels consisting of both cancer cells, and ECs lining the vessel walls have been observed in many cancer types.<sup>[42]</sup>

### Increased capabilities for invasion and metastasis

When tumors genetically or pharmacologically prevented from angiogenesis, cancer cells switch on a distinctive invasive growth program. Increased intravasation due to decreased integrity of the tumor vasculature is an insidious resistance mechanism to antiangiogenic therapy.

Upregulation of some epithelial mesenchymal transition (EMT)-related genes, such as twist and snail, and shifting of the epithelial to mesenchymal markers promote tumor metastasis.<sup>[43,44]</sup>

In untreated glioblastomas (GBMs), single cancer cells invade normal brain tissue whereas impairment of angiogenesis results in migration of multicellular layers and then metastasis.<sup>[35,45,46]</sup>

RCC treated with BVZ demonstrated accelerated growth capacity, and distant metastasis was observed as a result of tumor cells invasive profile.<sup>[47]</sup>

In addition, VEGF inhibition showed enhanced invasiveness metastasis of primary tumors in mouse models of GBM and pancreatic neuroendocrine carcinoma.<sup>[48]</sup>

### Autophagy

Autophagy, a reversible process having a prodeath or a prosurvival role in cancer, mediates antiangiogenic resistance.<sup>[49]</sup>

Autophagy, a cytoprotective adaptive response, provides a rescue mechanism for GBM cancer cells in unfavorable condition and maintains energy production leading to tumor growth and therapeutic resistance.<sup>[50]</sup> Activation



of AMPK and HIF-1 $\alpha$  pathways due to hypoxia-induced autophagy causes treatment resistance in GBM.<sup>[49]</sup>

These conflicting effects of autophagy on tumor cells are puzzling. According to the previous studies, autophagy is required for tamoxifen resistance. The activity of kinases confers resistance to tamoxifen. For example, a kinase called HSPB8 protects the cells against tamoxifen-induced death which results in tamoxifen resistance.<sup>[51]</sup> Autophagy induction is a mechanism of chemoresistance and is also observed in chemotherapeutic drug-treated esophageal cancer cells, enhancing the induction of apoptosis.<sup>[52]</sup>

### Lysosomal sequestration

Sunitinib administration without any interruption leads to resistance of tumor cells due to increasing intracellular lysosomal sunitinib accumulation and activity.<sup>[53]</sup> It has been reported that lysosomal sequestration can prevent access of the drug to the kinase domain of tyrosine kinase receptors present in the cytoplasm, thus participating in the loss of efficacy of the drug.<sup>[53]</sup> Resistance to sunitinib through lysosomal sequestration has been observed in renal cell cancer patients although this resistance is transient. So that, targeting lysosomal function will overcome sunitinib resistance.<sup>[54]</sup>

### Acquiring dormant and quiescent state

Tumor dormancy occurs with the counteraction of cell proliferation by apoptosis and impaired vascularization or immunosurveillance and cellular dormancy occurs with the cancer cells growth arrestment.<sup>[55]</sup>

Quiescence resulting in cancer cell survival after exposure to anticancer drugs contributes to disease recurrence.<sup>[56,57]</sup>

AIs induce long-term dormancy in tumor cells. Acquiring dormant state after antiangiogenic treatment and then recommencing the proliferation of tumor cells in the absence of angiogenic inhibitors lead to antiangiogenic resistance. Growth arrest due to active survival mechanisms providing dormant cells protection against chemotherapy and then doxorubicin resistance has been shown in breast cancer and colon cancer cells.<sup>[58]</sup>

### Glycosylation-Dependent Resistance in multidrug resistance and epithelial mesenchymal transition

According to recent evidence, angiogenic receptor signaling can also become activated independent of ligand binding.

EMT is related to the acquisition of multidrug resistance (MDR) phenotype; in other words, there is interplay between these two apparently distinct processes. Glycosylation, a posttranslational modification, is required in both phenomena. Disease relapse through MDR

mechanism is a fundamental cause of death in patients with small cell lung cancer, breast cancer, ovarian cancer, acute leukemia.<sup>[59]</sup>

Galectin-1 which is a glycan binding protein mediates the activation of VEGFR2 signaling after anti-VEGF intervention. This process is mediated by receptor glycosylation allowing the binding of galectin-1 that lead to VEGFR2 clustering and snoozed receptor internalization. Therefore, galectin-1 permissive glycosylation was associated with resistance to anti-VEGF therapy.<sup>[60]</sup>

## CONCLUSION

In spite of the primary promising results of angiogenic inhibitors, antiangiogenesis therapy encountered several challenges. Some cancers based on their stage of progression, genomic constitution and their microenvironment have the capacity to show refractory response to antiangiogenic agents. Although the majority of tumor types respond some cancer types avoid treatment through a variety of mechanisms.

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