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| RESEARCH ARTICLE

Drug Resistance to Anti-Angiogenic Therapy: Mechanisms, Clinical Implications, and Translational Strategies in Hepatocellular and Renal Cell Carcinoma.

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| ABSTRACT

Angiogenesis remains a fundamental hallmark of solid tumor growth and metastatic progression, and blocking the vascular endothelial growth factor (VEGF) pathway has changed how systemic therapy works for hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). However, the clinical benefits of anti-angiogenic therapy are frequently transient. Resistance arises from synchronized adaptive mechanisms that include redundant pro-angiogenic signaling, hypoxia-induced transcriptional reprogramming, metabolic reconfiguration, immune microenvironment alteration, and structural vascular evasion. Although the combination of VEGF blockade with immune checkpoint inhibitors (ICIs) has enhanced survival outcomes in pivotal trials such as IMbrave150 and CheckMate 9ER, sustained responses remain infrequent [1,2]. This review combines mechanistic and clinical evidence to create a comprehensive framework for anti-angiogenic resistance. We analyze ligand redundancy (FGF, PDGF, Ang-2), hypoxia-inducible factor (HIF)-mediated metabolic adaptation focused on glycolysis and lactate export, endothelial glycolytic regulation through PFKFB3, myeloid-driven immunosuppression, and structural resistance mechanisms such as vessel co-option and vasculogenic mimicry. We integrate these biological domains with phase III clinical trial data from HCC and RCC and suggest a translational roadmap that prioritizes orthogonal metabolic targeting, microenvironmental reprogramming, structural interception, and biomarker-guided adaptive scheduling at the top of the list during the vascular normalization window. Reconceptualizing resistance as a systems-level adaptive network establishes a basis for more resilient and region-specific therapeutic approaches.

| KEYWORDS

Anti-angiogenic resistance; VEGF blockade; Hepatocellular carcinoma; Renal cell carcinoma; Tumor microenvironment; Hypoxia-inducible factor; Endothelial metabolism; PFKFB3; Vessel co-option; Biomarker stratification

| ARTICLE INFORMATION

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1. Introduction: From Angiogenesis Inhibition to Adaptive Resistance

Angiogenesis is crucial for tumor growth exceeding 1–2 mm in diameter and for metastatic spread. VEGF-A signaling through VEGFR2 causes endothelial cells to grow, move, and become more permeable to blood vessels. This is the mechanistic basis for anti-angiogenic therapy. Monoclonal antibodies and multi-target tyrosine kinase inhibitors (TKIs) that target this pathway in the clinic have changed the way HCC and RCC are treated.

In unresectable HCC, the combination of atezolizumab and bevacizumab enhanced overall survival and progression-free survival relative to sorafenib in the IMbrave150 trial, thereby establishing VEGF–ICI combination therapy as the first-line standard of care [1]. In advanced renal cell carcinoma (RCC), combinations like nivolumab–cabozantinib (CheckMate 9ER) and lenvatinib–pembrolizumab (CLEAR) showed better survival rates than sunitinib [2,3]. These data substantiate that angiogenesis inhibition retains clinical efficacy.

Resistance to anti-angiogenic therapy is not merely a resurgence in VEGF expression. It is a coordinated, multi-compartment adaptive program that includes tumor cells, endothelial cells, stromal components, immune infiltrates, and the structure of the extracellular matrix. Blocking VEGF causes hypoxia, which stabilizes HIF-1α and HIF-2α and changes the way transcriptional networks work to encourage angiogenic redundancy, metabolic flexibility, immune suppression, and structural vascular adaptation [4].

The vascular normalization hypothesis gives us another way to think about things. Instead of completely destroying the blood vessels in a tumor, moderate VEGF inhibition temporarily improves blood flow and lowers interstitial pressure, which helps drugs get into the tumor and immune cells get into the tumor [5]. But this normalization window is always changing and only lasts for a short time. Too many or too long blockades could make hypoxia worse and speed up adaptive escape. Consequently, the primary challenge is not solely to inhibit angiogenesis but to prevent or intercept adaptive reprogramming.

In this review, we create a mechanistic classification of resistance that is divided into five domains that work together:

1. Excessive pro-angiogenic signaling
2. Adaptation of metabolism and transcription driven by hypoxia
3. Reprogramming the metabolism of endothelial cells
4. Immunological remodeling of the tumor microenvironment
5. Structural vascular escape (co-option and mimicry)

We subsequently amalgamate these mechanisms with clinical evidence and propose translational strategies to undermine resistance at various systemic levels.

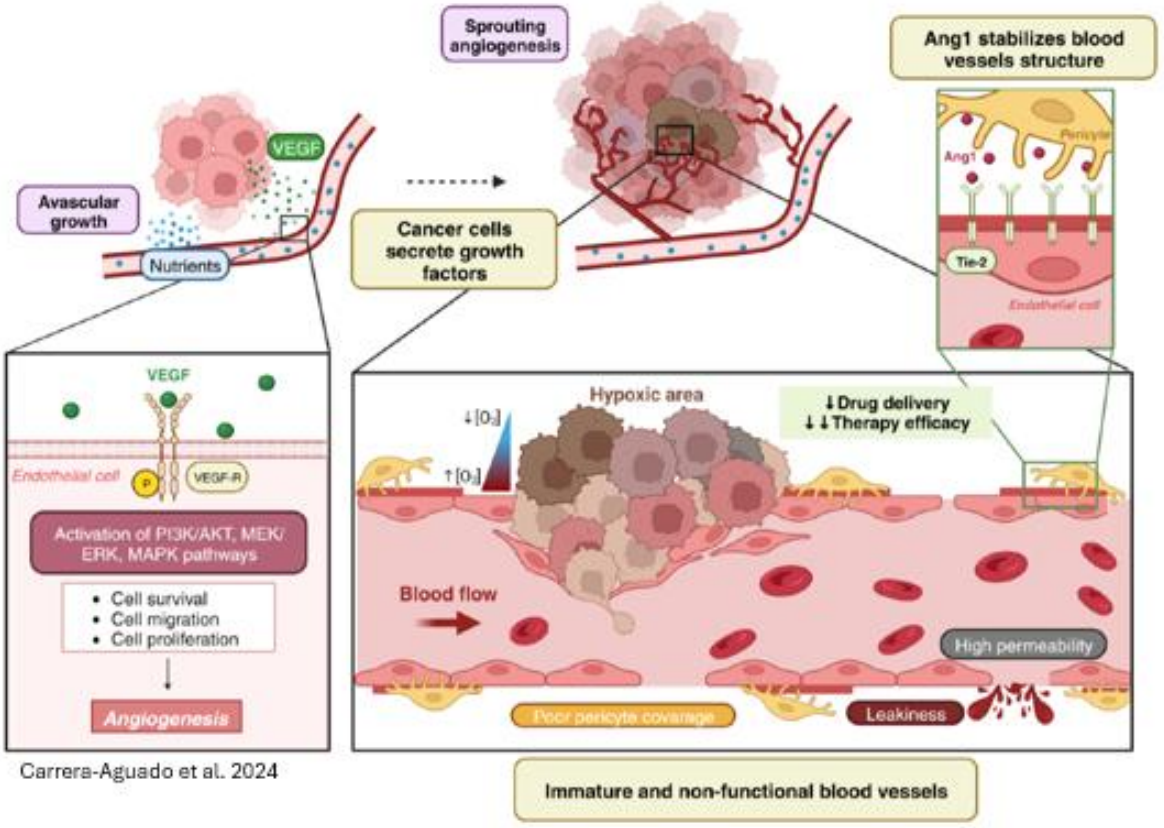

Figure 1. Tumor-Derived VEGF Activates VEGFR Signaling to Drive Sprouting Angiogenesis and the Formation of Immature, Leaky, Hypoxic Vasculature that Impairs Drug Delivery.

2. Redundant Pro-Angiogenic Signaling: Network Plasticity Beyond VEGF

Blocking VEGF-A stops VEGFR2-mediated angiogenic signaling, but it doesn't affect other ligand-receptor axes. Tumors quickly turn on other pro-angiogenic mediators, such as:

- Fibroblast growth factors (FGF/FGFR)

- Growth factor from platelets (PDGF/PDGFR)
- Angiopoietin-2 (Ang-2/Tie2)
- Growth factor from the placenta (PlGF)
- Tyrosine kinases for the MET and AXL receptors

Preclinical and translational studies indicate that hypoxia-induced Ang-2 and FGF2 expression can reinstate endothelial proliferation and pericyte recruitment subsequent to VEGF inhibition [6]. Under anti-VEGF pressure, MET and AXL signaling make invasive and pro-angiogenic phenotypes even more likely.

The partial redundancy of angiogenic pathways elucidates why multitarget TKIs are superior to single-pathway inhibition in specific contexts. In the REFLECT trial, Lenvatinib, which targets VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, showed better progression-free survival than sorafenib in HCC, but the overall survival gains were small [7]. This implies that pathway redundancy postpones but does not eradicate adaptive escape.

Importantly, angiogenic redundancy is not random. It is organized through transcriptional reprogramming induced by hypoxia, establishing a mechanistic connection to HIF signaling.

These coordinated hypoxia-driven adaptive programs are summarized in Figure 2.

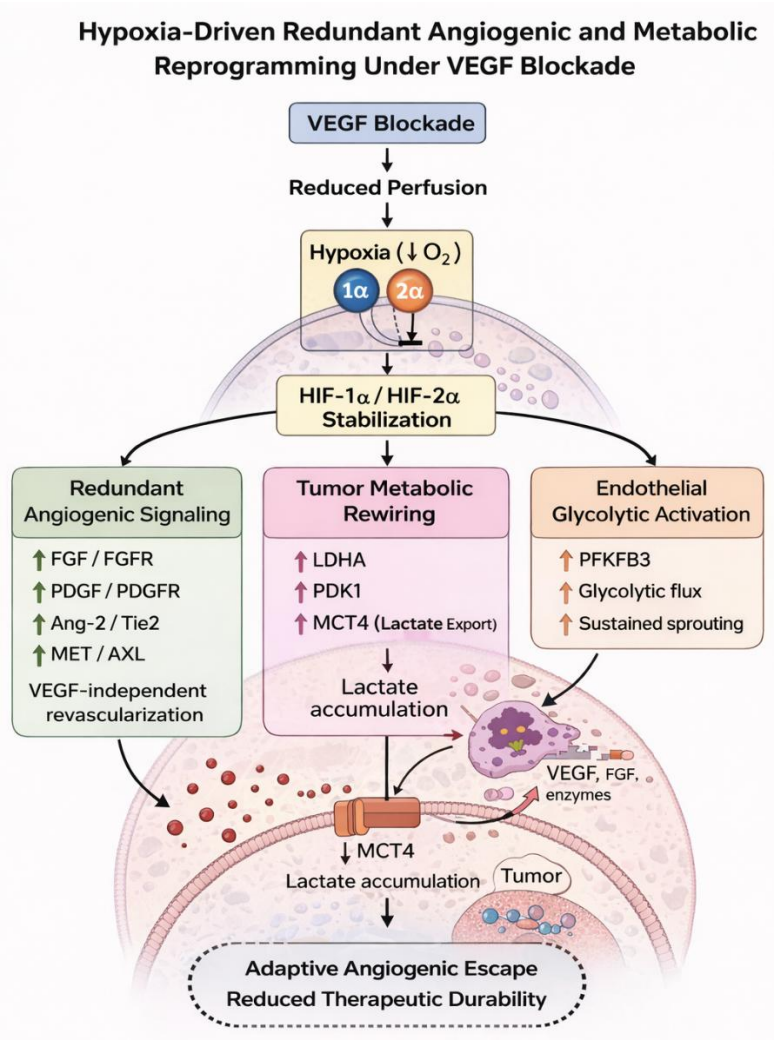

Figure 2. Hypoxia-driven redundant angiogenic and metabolic reprogramming under VEGF blockade. VEGF inhibition reduces tumor perfusion and induces hypoxia, leading to stabilization of HIF-1α and HIF-2α. HIF activation promotes compensatory upregulation of alternative pro-angiogenic signaling pathways, including FGF/FGFR, PDGF/PDGFR, Ang-2/Tie2, and MET/AXL, enabling VEGF-independent revascularization. Concurrently, tumor cells undergo metabolic rewiring characterized by increased glycolysis (LDHA, PDK1) and enhanced lactate export through MCT4, resulting in lactate accumulation within the tumor microenvironment. Lactate further reinforces pro-angiogenic and immunomodulatory signaling. Endothelial cells activate

glycolytic flux via PFKFB3, sustaining sprouting and vascular adaptation despite VEGF blockade. Together, these coordinated adaptive mechanisms drive angiogenic escape and reduce the durability of anti-angiogenic therapy.

3. Hypoxia–HIF Signaling and Metabolic Rewiring

Blocking VEGF lowers blood flow and makes hypoxia inside the tumor worse. When HIF-1α and HIF-2α are stabilized, they turn on transcriptional programs that help:

- Re-expression of VEGF
- Induction of PDGF and Ang-2
- Increased levels of glycolytic enzymes (LDHA, PDK1)
- Expression of monocarboxylate transporters (MCT1, MCT4)
- Drug efflux transporters (ABCB1, ABCG2)

This change in metabolism makes tumors more resistant to stress in blood vessels. In hypoxic microenvironments, the buildup of lactate serves as both a source of energy and a signaling molecule. Recent research shows that histone lactylation caused by lactate increases the expression of pro-angiogenic genes and causes macrophages to become more like M2 cells [8]. These macrophages release VEGF, FGF2, and enzymes that remodel the matrix, which helps angiogenic escape. Metabolic rewiring is not merely a downstream consequence of resistance but an active driver of adaptive escape.

Inhibiting LDHA or blocking MCT1/4 transporters to target lactate metabolism has shown promise in preclinical studies for reversing immunosuppressive and pro-angiogenic signaling networks [9]. These strategies constitute orthogonal interventions that may enhance VEGF blockade.

4. Endothelial Metabolic Reprogramming: The PFKFB3 Axis and Angiogenic Flux Control

In addition to tumor metabolic adaptation, endothelial cells undergo distinct metabolic reprogramming during angiogenesis. Even though it was thought that having more oxygen would help oxidative phosphorylation, sprouting endothelial cells mostly use glycolysis to make ATP, even when there is a lot of oxygen around [10].

6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is a glycolytic activator that makes fructose-2,6-bisphosphate, which speeds up the rate-limiting phase of glycolysis. This increases the activity of phosphofructokinase-1 and the flow of glycolysis. In preclinical tumor models, genetic or drug-based suppression of PFKFB3 in endothelial cells lowers the production of tip cells, stops abnormal sprouting, and partially restores the shape of blood vessels [10].

VEGF signaling significantly increases PFKFB3 expression, creating a feed-forward metabolic loop that keeps angiogenesis going. Endothelial cells may increase glycolytic flow in response to anti-VEGF pressure to keep migrating and living even though upstream receptors are blocked.

Targeting endothelial glycolysis is a different way of doing things. PFKFB3 inhibition doesn't stop ligand-receptor interactions; instead, it slows down the metabolic machinery needed for angiogenic sprouting. Early preclinical evidence suggests that partial glycolytic modulation may improve the effectiveness of VEGF inhibition while keeping normal vascular function [10].

However, shutting down glycolysis throughout the body poses safety issues, especially in tissues that turn over quickly. As a result, it will be necessary for clinical translation to use specific endothelium targeting or intermittent dose techniques.

5. Tumor Microenvironmental Reprogramming: Myeloid Recruitment and Immune Escape

Anti-angiogenic treatment has a lot of different effects on the immune system. VEGF brings in regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), but it stops dendritic cells from growing up. VEGF blockade may transiently enhance immune cell infiltration during the vascular normalization window [5]. Long-term hypoxia sends signals through the body that slow down the immune system.

Hypoxic tumor microenvironments make macrophages change into a pro-angiogenic M2-like phenotype, which is marked by the release of VEGF, FGF2, IL-8, and matrix metalloproteinases. The accumulation of lactate also facilitates macrophage polarization and the expression of PD-L1 [8].

Angiopoietin-2 also regulates the recruitment of myeloid cells via Tie2-expressing macrophages. This helps the body change its blood vessels and stop the immune system from attacking them [6]. Researchers are currently looking into therapeutic strategies that target myeloid signaling pathways like CSF1R, CCR2, CCR5, and TGF-β as a way to improve VEGF–ICI therapies. The aim of these therapies is to dismantle the stromal support network that facilitates the escape of angiogenic cells.

When used together, immune checkpoint inhibitors may greatly lower the immunosuppression that VEGF causes. In IMbrave150, the combination of atezolizumab and bevacizumab improved survival compared to sorafenib. This suggests that vascular modulation and immune activation work together to improve survival [1]. Blocking VEGF by itself doesn't work as well as using ICI and TKI together [1,2].

Dual VEGF–ICI strategies do not fully abrogate adaptive resistance, which shows that the microenvironmental reprogramming isn't being controlled well enough.

6. Structural Vascular Escape: Vessel Co-Option and Vasculogenic Mimicry

Structural resistance mechanisms may represent the most formidable limitation of VEGF-directed therapy, as they circumvent angiogenesis altogether.

6.1 Vessel Co-Option

In certain tumor contexts, particularly liver, lung, and brain metastases, malignant cells exploit pre-existing host vasculature rather than initiating de novo angiogenesis. Blocking VEGF doesn't work because vessel co-option allows tumors to grow without endothelial sprouting.

Histopathological analyses indicate that co-opted tumors exhibit a close alignment of cancer cells along native sinusoidal or parenchymal vessels, distinguished by minimal endothelial proliferation [11]. Vessel co-option has been linked to lower response rates to bevacizumab-containing treatments in colorectal liver metastases, which supports its role as a clinically important resistance mechanism [11,12].

Co-option is associated with invasive phenotypes and the upregulation of adhesion and motility pathways, suggesting that anti-invasive or anti-adhesion strategies may be requisite to restore angiogenic dependence.

6.2 Vasculogenic Mimicry

Vasculogenic mimicry (VM) refers to tumor cell-lined channels that can carry blood without endothelial cells. VM structures express matrix remodeling proteins and stemness-associated transcription factors, including FOXC2 and VE-cadherin-like markers [13].

VM does not necessitate endothelial VEGFR2 signaling; thus, VEGF blockade does not impair these pseudo-vascular networks. New data suggest that targeting pathways or transcriptional regulators related to EMT, like FOXC2, may stop VM from forming [13]. However, there are still no clinical inhibitors that have been tested.

Vessel co-option and VM are both architectural changes that completely avoid angiogenic targeting. To stop these processes from happening, we will probably need biomarker-guided patient stratification and combination approaches.

7. Clinical Integration: Lessons from Phase III Trials

A mechanistic understanding must be situated within clinical evidence.

7.1 Hepatocellular Carcinoma

The IMbrave150 trial showed that atezolizumab plus bevacizumab worked better than sorafenib for people with unresectable HCC in terms of overall survival and progression-free survival [1]. This combination combines blocking VEGF with blocking PD-L1, using vascular normalization to boost immune infiltration.

The REFLECT trial demonstrated that lenvatinib is a non-inferior alternative to sorafenib, exhibiting enhanced progression-free survival while maintaining comparable overall survival [7]. These results highlight the limited advantage of extensive kinase inhibition aimed at FGFR and PDGFR, alongside VEGFR.

More recently, immune checkpoint-based combinations like durvalumab-tremelimumab (the STRIDE regimen) have demonstrated improved overall survival compared to sorafenib. This gives some patients an immunotherapy option that doesn't use VEGF.

Even with these improvements, the median survival rate is still low, and progression is still common because of ongoing resistance mechanisms.

7.2 Renal Cell Carcinoma

In advanced RCC, VEGF-targeted therapy has been fundamental for an extended period, owing to VHL-mediated HIF stabilization. Combination strategies have changed what first-line therapy means. CheckMate 9ER demonstrated that the combination of nivolumab and cabozantinib enhanced progression-free and overall survival in comparison to sunitinib [2]. The

CLEAR study showed that lenvatinib plus pembrolizumab worked better than sunitinib [3]. These treatment plans block both the VEGF pathway and immune checkpoints, which helps fight both angiogenic and immunologic resistance.

Long-term follow-up, on the other hand, shows that full responses are still rare and that most patients will eventually become resistant. The mechanistic domains delineated above probably function in conjunction, rather than in isolation, to facilitate progression.

8. Regional Sequencing Strategies and Real-World Implementation

Even though randomized trials set the first-line standards, the order of treatments in the real world varies by region because of epidemiology, comorbidity patterns, and the healthcare system.

8.1 Asia–Pacific Context

Countries in the Asia-Pacific region have the highest rate of hepatocellular carcinoma in the world. This is mostly because of chronic hepatitis B virus infection. In some areas, multi-kinase inhibitors like lenvatinib and sorafenib have been widely used in the past because they got regulatory approval faster and were cheaper [7]. Even after IMbrave150 showed that atezolizumab–bevacizumab was the best first-line treatment [1], access to immunotherapy combinations has remained variable due to reimbursement constraints and healthcare infrastructure disparities.

Also, in high-volume centers, mandatory endoscopic screening for varices before starting bevacizumab-containing regimens can slow down the start of treatment. These operational realities affect decisions about sequencing and may have unintended effects on results.

8.2 Western Practice Patterns

In Europe and North America, rapid integration of ICI–VEGF combinations has occurred following guideline endorsements from EASL, AASLD, and ASCO. In renal cell carcinoma (RCC), ICI–TKI combinations have predominantly supplanted VEGF monotherapy in the first-line setting subsequent to CheckMate 9ER and CLEAR [2,3].

Nonetheless, the sequencing of second-line therapy following progression on VEGF–ICI combinations is still unresolved. Alternative TKIs like cabozantinib or lenvatinib are options, but there is no prospective proof of the best order or patient selection.

The fact that things are different in different parts of the world shows that we need treatment algorithms that are based on biomarkers and systems, not just global sequencing.

9. Translational Roadmap: Intercepting Adaptive Resistance

The ongoing resistance despite dual VEGF–ICI strategies indicates that incremental pathway inhibition is inadequate. A systems-level approach is necessary. We suggest five translational pillars that depend on each other:

9.1 Orthogonal Metabolic Targeting

Hypoxia-induced lactate accumulation and glycolytic reprogramming serve as pivotal mechanisms in resistance [4,8]. Targeting LDHA, PDK1, or MCT1/4 transporters may diminish metabolic plasticity and decrease macrophage polarization. In a similar way, partial PFKFB3 inhibition of endothelial glycolysis may stop pathological sprouting while keeping the blood vessels healthy [10]. Future trials ought to assess metabolic adjuncts integrated with VEGF–ICI backbones through early-phase window-of-opportunity designs and correlational metabolic imaging.

9.2 Microenvironmental Reprogramming

Myeloid cell recruitment and immunosuppressive macrophage polarization facilitate angiogenic escape. Drugs that target the CSF1R, CCR2/CCR5, or TGF-β pathways could change the tumor microenvironment and make ICI more responsive. Combination designs need to put safety first and not have too much overlapping toxicity with VEGF blockade.

9.3 Structural Resistance Interception

For tumors exhibiting vessel co-option or vasculogenic mimicry, VEGF blockade alone is inadequate [11–13]. Histological and radiomic methodologies may facilitate the identification of co-option-dominant phenotypes. Anti-invasive strategies that target MET/AXL signaling or transcription factors linked to epithelial-mesenchymal transition (EMT) could bring back angiogenic dependence. Structural resistance biomarkers are an essential unmet requirement for individualized treatment.

9.4 Vascular Normalization Guided Adaptive Scheduling

The vascular normalization window changes depending on the patient [5]. Excessive inhibition of VEGF signaling may worsen hypoxia and hasten resistance. Dynamic contrast-enhanced MRI and perfusion CT are two examples of advanced imaging techniques that, along with circulating biomarkers like soluble VEGFR2 and Ang-2, could help doctors figure out how to change the dose of a drug. Future trials that include imaging-guided strategies for increasing and decreasing doses may improve how well different treatments work together.

9.5 Systems-Level Analytics and Equity-Aware Implementation

Implementation science and predictive modeling frameworks can help with patient stratification and resource allocation, especially in places where immunotherapy is hard to get. Combining clinical, imaging, and lab data into machine learning pipelines could help find groups of people who are most likely to benefit from certain combinations or sequencing strategies. Multi-cohort transcriptomic meta-analyses have shown that angiogenesis-associated gene programs and mesenchymal remodeling signatures are consistently more common in tumors that don't respond to treatment. This supports the use of mechanism-anchored biomarker strategies instead of just data-driven gene lists [14]. Due to differences in cancer care infrastructure around the world, these kinds of approaches must take equity into account.

9.6 AI-Driven Biomarker Stratification and Adaptive Resistance Modeling

Biomarker frameworks need to include multi-omic signatures in addition to single-gene predictors because the molecular diversity that causes anti-angiogenic resistance makes it hard to find them. Hypoxia-driven angiogenic redundancy, endothelial metabolic reprogramming, myeloid infiltration, and structural vascular escape are transcriptionally encoded programs, not just single events along a pathway. AI and ML methods provide scalable tools to help us understand these complex resistance networks and find groups of patients with different adaptive paths.

Recent meta-analyses of transcriptomic data from multiple groups have shown that tumors that don't respond to treatment always have more gene programs related to angiogenesis and mesenchymal remodeling. This backs up the idea that mechanism-anchored biomarker strategies are better than gene lists that are only based on data [14]. These models have genes that respond to low oxygen levels (HIF targets), enzymes that break down glucose (LDHA, PDK1), metabolic regulators for endothelial cells (PFKFB3), and markers that suppress the immune system (CSF1R, CCR2, PD-L1). Researchers can now group tumors into three types: angiogenic-dominant, immune-evasive, or metabolically adaptive.

Predictive analytics frameworks that amalgamate clinical variables, imaging parameters, and molecular profiling have proven viable in outcome modeling and population-level oncology analysis, creating a scalable platform for resistance-informed therapeutic stratification [15,16]. Integrating these computational methodologies into forthcoming, biomarker-enhanced trial designs may facilitate dynamic risk modeling, rational treatment sequencing, and the expedited identification of adaptive resistance. Integrative modeling that merges radiomic perfusion signatures with transcriptomic resistance modules could enhance patient selection for VEGF–ICI combinations compared to metabolically or myeloid-targeted adjunct strategies, thereby aligning therapeutic intensity with predominant resistance phenotypes.

In future trials, it's important to use biomarkers to test AI-driven stratification to make sure it doesn't overfit and works in different places and with different types of people. It is especially important to be aware of equity when developing models for hepatocellular carcinoma because the disease has different causes in different areas, which affects how the tumor grows and how easy it is to get treatment.

Integration of systems biology with computational modeling may enable patient-specific modulation of anti-angiogenic therapy, transforming resistance prediction from retrospective observation into prospective therapeutic guidance.

10. An Integrated Model of Anti-Angiogenic Resistance

Resistance to anti-angiogenic therapy ought to be regarded as an adaptive network rather than a linear pathway failure. Blocking VEGF lowers perfusion. Less perfusion makes hypoxia worse. Hypoxia stabilizes HIF-1α and HIF-2α.

HIF activation drives:

- Expression of alternative angiogenic ligands
- Rewiring of glycolytic and lactate metabolism
- Bringing in myeloid cells and lowering the immune response
- Invasive and structural adaptation (co-option, VM)

These domains support each other, creating a resistance circuit that stays stable on its own. Targeting a single node may temporarily impede progress, but a lasting advantage probably necessitates the synchronized disruption of several adaptive

layers. This perspective on the system sees anti-angiogenic resistance as an ecological adaptation in the tumor microenvironment.

11. Conclusion

Anti-angiogenic therapy has fundamentally transformed the treatment of HCC and RCC. Significant survival benefit is shown by landmark trials like IMbrave150, CheckMate 9ER, and CLEAR that show that blocking VEGF, especially when combined with immune checkpoint blockade, works [1–3]. But resistance is still the norm, not the exception. Redundant ligand-receptor signaling, metabolic adaptation driven by hypoxia, endothelial glycolytic flux, immunosuppression in the microenvironment, and structural vascular escape all work together to make long-term control less effective.

To move forward, we need to change from pathway-level inhibition to system-level interception. Orthogonal metabolic targeting represents a rational next step, microenvironmental reprogramming, structural resistance identification, and adaptive normalization-guided scheduling. Anti-angiogenic therapy may evolve from short-term disease control toward more durable and biologically informed therapeutic benefit by integrating mechanistic depth with biomarker-driven trial design and region-sensitive implementation strategies.

Ultimately, long-term control of cancers that depend on angiogenesis will need a coordinated attack on metabolic, immunologic, and structural resistance circuits, not just a stronger VEGF blockade. To turn anti-angiogenic therapy from temporary disease modulation into long-term therapeutic control, we need to move toward adaptive, biomarker-informed, multi-domain intervention strategies.

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