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REVIEW

Unraveling vascular mechanisms in melanoma: roles of angiogenesis and vasculogenic mimicry in tumor progression and therapeutic resistance

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ABSTRACT Melanoma, the most aggressive form of skin cancer, remains a significant clinical challenge due to the high metastatic potential and drug resistance. This review explores the pivotal roles of angiogenesis and vasculogenic mimicry in melanoma progression and treatment resistance. Angiogenesis, driven primarily by VEGF/VEGFR signaling, is critical for tumor sustenance but is often insufficient under hypoxic conditions, prompting melanoma cells to adapt by forming vascular-like structures (i.e., vasculogenic mimicry). These structures enable melanoma cells to mimic endothelial functions and are linked to increased metastasis and poor prognosis. Molecular drivers, including VE-cadherin, EphA2, and hypoxia-inducible factors, have been identified as key regulators of these processes. Current anti-angiogenic agents have limited efficacy in advanced/metastatic melanoma due to tumor plasticity and the interplay between angiogenesis and vasculogenic mimicry. The review highlights the need for therapeutic strategies targeting both mechanisms, emphasizing the importance of combination treatments to overcome resistance. Future research should aim to elucidate the molecular underpinnings of angiogenesis and vasculogenic mimicry to improve melanoma management and patient outcomes.

KEYWORDS Melanoma; angiogenesis; vasculogenic mimicry

Introduction

Melanoma, the deadliest form of skin cancer, has seen a rise in incidence and prevalence over the past decade[1]. Although mortality rates have decreased due to improved early diagnosis and immune checkpoint inhibitors (ICIs), melanoma remains a highly aggressive cancer originating from melanocytic precursors with significant potential for local and metastatic spread[2]. Melanoma exhibits abnormal growth due to mutations in key regulatory genes, disrupting normal responses to keratinocyte signals[3]. The classical progression model of melanoma involves an initial stage of nevus formation followed by a radial growth phase and potentially a vertical growth phase, where melanocytes invade the dermis, posing a high risk of metastasis[4,5]. Approximately 25% of melanoma cases develop from nevi and 5%–15% of patients have a family history of the disease[6]. Early-stage melanoma can often be cured with surgical removal but metastasis frequently occurs after initial treatments, causing disease recurrence[7-9].

The superficial spreading type (SSM) is the most common histopathologic pattern of melanoma[10,11]. UV radiation, which directly damages DNA, is a major risk factor, along with acquired and congenital nevi[12,13]. As the primary tumor grows and nutrient diffusion becomes limited, a specialized network of blood vessels is essential for providing substrates necessary for cancer cell survival and growth[14]. Advanced melanoma prognosis remains poor despite the availability of treatments like immunotherapy and targeted therapies[7,9]. Uveal melanoma, although less common than skin cancer,

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leads to significant morbidity and mortality with nearly 50% of patients succumbing to metastatic disease[15]. While cutaneous melanoma spreads through lymphatics or blood vessels, uveal melanoma, arising in capillary-rich tissues, exemplifies hematogenous cancer dissemination[16]. The neovasculature within tumors is often aberrant and incomplete, characterized by distorted, dilated, and leaky vessels, insufficient pericyte coverage, abnormal endothelial cell proliferation, and an uneven distribution within the tumor tissue. These features contribute to tumor cell dissemination *via* the vascular system[17-20]. The angiogenic switch is activated by cancer cells and is driven by an imbalance favoring angiogenesis[21]. Melanoma cells first induce the extension of pre-existing vessels, then recruit bone marrow progenitors to hypoxic regions within the tumor microenvironment (TME) and can adopt an endothelial-like phenotype, a phenomenon known as vascular or vasculogenic mimicry (VM), integrating directly into the vessel structure[22].

VM, is the formation of perfusable networks by aggressive tumor cells that provide an alternative blood supply to tumor growth[23-25]. This mechanism is associated with distant metastases, high recurrence rates, and poor survival outcomes in various cancers, including melanoma[25,26]. Recent research has identified key pathways and mechanisms involved in VM, such as VE-cadherin and Eph receptor A2 (EphA2) in vascular signaling, hypoxia, and the MEK/ERK pathway under specific conditions[27]. Given the significant influence of angiogenesis and VM on melanoma progression, treatment strategies, and patient prognosis, extensive research is needed to understand the mechanisms underlying these processes and identify potential therapeutic targets.

Angiogenesis in melanoma

Melanoma progression through the vertical growth phase is characterized by high angiogenic activity, enabling metastasis. During this phase, melanoma cells invade lymphatic vessels and spread to distant organs, such as the lungs, liver, and brain. This proliferation depletes oxygen and nutrients, leading to hypoxia, which further drives angiogenesis[28-31].

Angiogenesis in melanoma occurs in the following two phases: the avascular phase, relying on diffusion for metabolite transport; and the vascular phase, during which new vessels form from capillaries and post-capillary venules. This vascularization allows local invasion and hematogenous metastases[32,33].

The angiogenic switch, which is driven by an imbalance favoring pro-angiogenic factors, activates quiescent vasculature. Tumor cells release large amounts of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), which was the first identified factor with angiogenic potential. VEGF and other growth factors act *via* autocrine and paracrine mechanisms, stimulating endothelial cell proliferation and enabling tumor growth, invasion, and metastasis[21,34,35].

VEGF family and its role in melanoma angiogenesis

Initially identified as a vascular permeability factor (VPF), VEGF is now recognized as a multifunctional peptide critical for endothelial cell proliferation, migration, and survival in both physiologic and pathologic conditions[36]. The VEGF family includes VEGF-A, placental growth factor (PlGF), VEGF-B, VEGF-C, and VEGF-D, which with their receptors are primary regulators of angiogenesis, surpassing other mediators, like fibroblast growth factor (FGF)-2, hypoxia-inducible factor-1 alpha and beta (HIF-1α/β), and tumor necrosis factor-alpha (TNF-α), VEGF-A also induces pro-angiogenic activities, such as the expression of endothelial proteases, including matrix metalloproteinases (MMPs), urokinase-type plasminogen activator (uPA), and tissue-type plasminogen activator (tPA). The VEGF family members are homodimeric glycoproteins, each of which are expressed as diverse variants that result from alternative splicing mechanisms, further enhancing functional versatility[37].

VEGF-A is secreted by various cell types, including endothelial and tumor cells, as well as macrophages. VEGF-A has a crucial role in various biological processes, including embryonic development, vascular formation, postnatal angiogenesis, bone growth, tissue repair, and reproductive functions[37]. Studies have shown a positive correlation between increased immunohistochemical expression of VEGF-A and melanoma progression, particularly from primary to metastatic stages[38-40]. VEGF-A also contributes to immune exhaustion in the TME. CD146-positive tumors circumvent anti-VEGF-A therapy by secreting soluble CD146 (sCD146), suggesting a collaboration between VEGF-A and sCD146 to create an immunosuppressive microenvironment[41] (**Figure 1**).

PlGF is a crucial pro-angiogenic factor within the VEGF family. Its isoforms, PlGF1 and PlGF2, are expressed by melanoma cells[42] and, besides acting by binding to the VEGF receptor-1 (VEGFR-1), also interacts with neuropilin-1 (NRP-1)

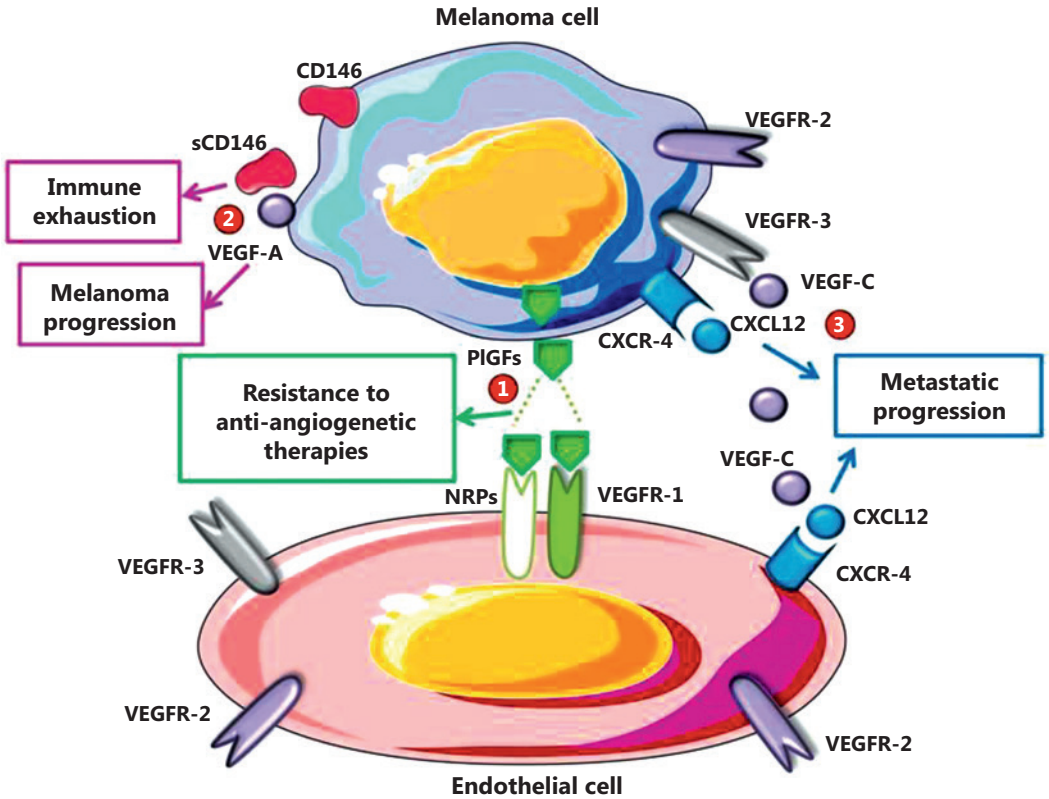

Figure 1 VEGF/VEGFR signaling axis in melanoma progression: VEGFRs are expressed by melanoma and endothelial cells, regulating angiogenesis and affecting tumor growth, cell proliferation, migration, metastasis, and resistance to therapy. (1) PlGF1 and PlGF2 are expressed by melanoma cells, and in addition to binding VEGFR-1, also interact with NRP-1 and NRP-2 on endothelial cells. Elevated PlGF secretion and enhanced NRP-1 expression have been associated with resistance to anti-angiogenic therapies. (2) VEGF-A and sCD146 cooperate to establish an immunosuppressive microenvironment and immune exhaustion. (3) Overexpression of VEGF-C in melanoma promotes upregulation of the chemokine receptor, CXCR-4, which is activated by CXCL12 produced by endothelial cells, creating a synergy that drives the metastatic progression of the tumor. The figure was partly generated using Servier Medical Art, provided by Servier and licensed under a Creative Commons Attribution 3.0 unported license (https://smart.servier.com/). CXCL12, chemokine ligand; CXCR-4, chemokine receptor; PlGF, placental growth factor; NRPs, neuropilins; sCD146, soluble CD146; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

and neuropilin-2 (NRP-2) on endothelial cells (ECs). Its ability to form heterodimers with VEGF-A enables PlGF to indirectly stimulate the VEGFR-2 receptor on ECs[43]. This pathway significantly enhances tumor angiogenesis by acting on pre-existing ECs and mobilizing VEGFR-1-positive hematopoietic precursors from the bone marrow[44]. It also enhances vascular maturation by acting on VEGFR-1-expressing smooth muscle cells and pericytes[45]. PlGF promotes tumor growth through an autocrine mechanism, facilitating tumor growth and neovascularization in melanoma models. It has been also involved in melanoma metastases to bone marrow through activation of VEGFR-1[46]. Moreover, increased PlGF secretion and upregulated NRP-1 expression have been linked to resistance to anti-angiogenic therapies, particularly those targeting VEGF-A[47] (**Figure 1**).

VEGF-B, secreted by heart and skeletal muscle tissues, is involved in inflammatory angiogenesis and is linked to some tumors, like colon adenocarcinoma and hepatocellular carcinoma[48,49]. Elevated VEGF-B expression leads to increased vascular leakiness, hypoxia, and tumor-infiltrating macrophages, promoting metastasis and worse survival in patients with lung squamous cell carcinoma and non-ocular melanoma[50].

VEGF-C and VEGF-D are crucial for embryonic lymphatic vessel formation and lymphangiogenesis, respectively. VEGF-C and VEGF-D have been extensively studied in relation to disease, particularly cancer progression and

metastasis through lymphangiogenesis. Conflicting data on the roles in lymphatic vessel formation suggest a need for further research[37]. VEGF-C interacts with VEGFR-3, a receptor present on lymphatic endothelial and melanoma cells, leading to phosphorylation and activation of signaling pathways. Overexpression of VEGF-C in melanoma promotes upregulation of the chemokine receptor, CXCR-4, which directs leukocyte migration in response to the chemokine ligand, CXCL12, which is produced by lymphatic endothelial and stromal cells within the TME (**Figure 1**). This gradient drives the metastatic progression of the tumor[51].

VEGF receptors (VEGFRs) comprise a family of three receptors: VEGFR-1/FLT-1 and VEGFR-2/KDR/FLK-1, which are primarily involved in angiogenesis; and FLT-4/VEGFR-3, which has roles in hematopoiesis and lymphogenesis[52].

VEGFR-1 is a high-affinity receptor for VEGF-A, PlGF, and VEGF-B, which are expressed in ECs, macrophages, and hematopoietic stem cells[53]. VEGFR-1 was initially believed to limit angiogenesis due to low tyrosine kinase activity, but VEGFR-1 supports pathologic vascular formation by binding VEGF-A and PlGF. The soluble variant, sVEGFR-1, is secreted into the extracellular space and is increasingly recognized for anti-angiogenic and anti-inflammatory effects[37,54].

VEGFR-2 is central to angiogenic processes and interacts with VEGF-A, VEGF-C, and VEGF-D. VEGFR-2 regulates vascular permeability, cellular proliferation, migration, and survival through signaling pathways, such as PLCγ, PKC, PI3K, and MAPK. VEGFR-2 is often overexpressed in cancers, including melanoma, lymphoma, and breast and ovarian cancers, underscoring the role in pathologic angiogenesis[54].

The VEGF/VEGFR signaling axis has a central role in melanoma progression, modulating angiogenesis and influencing tumor growth, cellular proliferation, migration, metastasis, and resistance to therapy[55]. VEGF-A is crucial in melanoma cell proliferation with overexpression linked to increased cell growth through activation of receptors on endothelial and melanoma cells[56]. Blocking VEGF-A or antagonizing VEGFR-1 effectively hinders melanoma growth, highlighting MAPK, PI3K, and Wnt5a/β-catenin/AKT as crucial signaling pathways that could be targeted to limit melanoma expansion[57,58].

Despite VEGF-A being the most significant factor in angiogenesis, other endogenous factors, such as FGF-2, HIF-1α, transforming growth factor-beta (TGF-β), interleukin-8 (IL-8), angiopoietin-1 and -2 (Ang-1 and Ang-2), platelet-derived growth factor (PDGF), MMPs, and fibrinolytic system, also function as mediators of this process[59].

Role of angiopoietins in tumor angiogenesis

Ang1 and Ang2 are cytokines that drive tumor angiogenesis by interacting with tyrosine kinase receptors (TIE1 and TIE2), which are found in blood and lymphatic endothelium[60]. The orphan receptor, TIE1, is overexpressed in tumor vessels and is flow-regulated[61], while TIE2 is activated by Ang1 and Ang2. Ang1 ensures vascular integrity and supports endothelial cell migration, adhesion, and survival, stabilizing new vessels[62]. Conversely, Ang2 disrupts vessel stability by dissociating perivascular cells, acting antagonistically to Ang1, particularly during vascular remodeling[63]. Elevated Ang2:Ang1 ratios correlate with increased angiogenesis in cancer[64]. Ang1 expression is not linked to malignancy grade[65], whereas Ang2 overexpression is associated with higher malignancy, also in cutaneous melanoma[66]. Advanced melanoma (stages III and IV) has significantly higher Ang2 serum levels than earlier stages and healthy controls[67]. It has also been suggested that Ang1 promotes choroidal melanoma proliferation *via* the Akt/mTOR pathway[68], while Ang2 is highly expressed in uveal melanoma, particularly in high-risk tumors, highlighting its potential as a therapeutic target[69], moreover Ang-2 in the presence of VEGF-A promotes angiogenesis[70] (**Table 1**).

Hypoxia and HIF-1: implications for melanoma angiogenesis

The TME, which is characterized by hypoxia, ischemia, acidosis, and elevated interstitial pressure, promotes angiogenesis and lymphangiogenesis through the release of growth factors and cytokines[85,86]. Hypoxia, a hallmark of solid tumors, contributes to drug resistance, angiogenesis, aggressiveness, and recurrence[87,88] by activating HIF-1, a key regulator of angiogenesis, metabolism, proliferation, and metastasis[89,90]. The relationship between melanoma and HIF-1α has been explored in various studies[91,92]. Martínez-García et al. conducted a prospective multicenter cohort study focusing on the clinical staging and correlation between increased HIF-1α expression and melanoma cells[93]. Moreover, hypoxia promotes cell cycle arrest and compensatory angiogenesis, leading to chemotherapy and anti-angiogenic treatment resistance, respectively[94,95]. HIF-1α participates in several signaling pathways, including PI3K/Akt/mTOR, RAS/RAF/MEK/ERK, JAK/STAT, and Wnt/β-catenin[71,96-98]. Alterations in these pathways influence critical processes in melanoma, such as tumor growth

Table 1 Key molecular drivers of angiogenesis in melanoma

Molecular driver	Role in angiogenesis	References
Angiopoietins (Ang1/Ang2)	– Ang1: stabilizes vessels, supports EC migration, adhesion, and survival *via* TIE2 activation – Ang2: destabilizes vessels, promotes remodeling, and antagonizes Ang1 – High Ang2/Ang1 ratio correlates with increased angiogenesis and malignancy	62,70
HIF	– Activates transcription of VEGF and other pro-angiogenic genes	71
IL-8	– Enhances endothelial cell migration – Modulates vascular permeability of endothelial cells – Activates MMP-2 to promote tumor invasion and angiogenesis	72,73
MMPs	– Facilitate the release of pro-angiogenic factors by degrading extracellular matrix components	74-79
TGF-β	– Induces angiogenesis by upregulating angiogenic mediators, such as FGF-2 and VEGF-A – Enhances IL-8 expression in melanoma cells – Promotes angiogenesis in murine xenograft models	80,81
FGF-2	– Induces VEGF-dependent neovascularization – Enhances EC proliferation and survival	82
PDGF	– Recruits pericytes and fibroblasts – Stimulates angiogenesis *via* paracrine and autocrine signaling – Supports vascular stabilization and tumor progression	83
uPA/uPAR system	– Promotes angiogenesis through uPAR-enriched extracellular vesicles (EVs) derived from melanoma cells, stimulating endothelial cell proliferation, migration, and tube formation	84

regulation, angiogenesis, metabolism, cell movement, and programmed cell death[99]. Moreover, VEGF is among the primary target genes regulated by HIF-1. As the principal mediator of angiogenesis, VEGF and its receptors are closely linked to the expression of HIF-1α. Under hypoxic conditions, HIF-1α translocates to the nucleus, where HIF-1α induces transcription of various downstream genes, including VEGF[71,98] (**Table 1**).

Others key molecular drivers of angiogenesis in melanoma

In a clinical study melanoma patients exhibited higher IL-8 levels compared to healthy subjects with a correlation observed between elevated IL-8 levels and disease progression[72]. Tumor-derived IL-8 operates by binding to IL-8 receptors (CXCR1 and CXCR2) through an autocrine mechanism, stimulating tumor cell growth and proliferation, while also promoting endothelial cell migration[73]. Conversely, IL-8 derived from ECs facilitates melanoma cell migration. IL-8 induces actin fiber formation by activating G protein-coupled receptors on ECs, causing cell retraction and creating gaps between ECs, thereby modulating vascular permeability. Experimental studies have shown that IL-8 overexpression in poorly vascularized, non-metastatic melanoma (MM) cells increases angiogenesis, accelerates tumor growth, and enhances metastatic potential[100,101]. Multiple studies have conclusively shown that IL-8 produced by tumor cells directly contributes to melanoma progression, whereas EC-derived IL-8 further facilitates the migratory capacity of melanoma cells. Moreover, tumor-derived IL-8 has been shown to stimulate the migration of ECs[80].

MMPs are a family of zinc-dependent endopeptidases that have crucial roles in invasiveness, wound healing, tissue remodeling, and angiogenesis[102]. Physiologically, MMPs are minimally expressed in benign melanocytes. Therefore, the expression of MMPs indicates an advanced stage of disease[103].

MMPs have a pivotal role in angiogenesis by facilitating the release and activation of key pro-angiogenic factors, including VEGFs, FGFs, and TGF-β, from the extracellular matrix (ECM) through various mechanisms[74-76]. For example, MMP-2 contributes to degradation of the ECM proteoglycan, decorin, leading to the liberation of latent TGF-β. Both MMP-2 and MMP-9 can also activate TGF-β by proteolytically cleaving the latency-associated peptide (LAP)[77]. Similarly, FGF-2, which is localized within the endothelial basement membrane, is sequestered in the ECM in a biologically inactive form. Activation of FGF-2 necessitates proteolytic cleavage of heparan sulfate proteoglycans (key anchoring components for

FGF-2), a process mediated by MMPs[74]. These factors serve as signaling molecules, binding to ECs and triggering blood vessel sprouting into the spaces cleared by the action of MMPs[78]. The elevated expression of MMP-2 and MMP-9 is strongly associated with higher metastasis rates and reduced patient survival. Additionally, these MMPs contribute to radial tumor growth and promotion of angiogenesis in MM[78,79].

TGF-β has a dual role in angiogenesis, acting as a stimulator and inhibitor depending on the microenvironment, interacting with other signaling pathways, and disease progression[104]. TGF-β promotes angiogenesis by upregulating angiogenic factors, like FGF-2, VEGF-A, and angiopoietin-1, incorporating endothelial progenitor cells (EPCs) into new vessels[81] or facilitating endothelial-to-mesenchymal transition (EndMT), enhancing angiogenic potential[105]. A recent investigation demonstrated that TGF-β1 upregulates IL-8 expression in human melanoma cells and enhances angiogenesis in murine xenograft models[80].

FGF-2 is a pro-angiogenic cytokine involved in tumorigenesis *via* an interaction with FGFRs. Invasive melanomas express FGF-2 mRNA, unlike melanoma *in situ* or benign nevi[106]. Antisense oligonucleotides targeting FGF-2 suppress tumor growth and angiogenesis *in vivo*[107]. FGF-2 also induces VEGF-dependent neovascularization in melanoma models[82] and promotes angiogenesis during the transition to the vertical growth phase by regulating endothelial cell proliferation through autocrine and paracrine mechanisms. MMPs facilitate the release of matrix-bound FGF-2, driving endothelial proliferation and vascular tube formation[80].

The members of the PDGF family are composed of five isoforms (PDGF-AA, -BB, -AB, -CC, and -DD) that interact with PDGF tyrosine kinase receptors (PDGFRs) α and β to mediate various effects. Initially identified in platelets, PDGF is produced by endothelial and melanoma cells[108]. PDGF supports tumor progression in melanoma by recruiting pericytes and fibroblasts and enhancing angiogenesis *via* paracrine and autocrine signaling. PDGF and PDGFR have a critical role in modulating the interaction between pericytes and ECs. Upon ligand binding, PDGFR undergoes dimerization and autophosphorylation, subsequently initiating signal transduction primarily through the PI3K pathway, which is essential for ECs migration. The PDGF/PDGFR axis facilitates the recruitment of pericytes to the immature, newly forming vasculature during angiogenesis. Pericytes typically ensheath the abluminal surface of ECs, contributing to vascular stabilization and angiogenic processes, in part through the production of VEGF[83]. PDGF-BB and -DD with PDGFR-β promote angiogenesis, while PDGF-AA and PDGFR-α have anti-angiogenic effects[70]. A relevant function in the metastatic switch of melanoma cells has recently been suggested for PDGF-CC through a newly described interaction with NRP-1 that activates specific signal transduction pathways and transcription factors, after which PDGF-CC promotes an invasive phenotype, including VM[109]. This mechanism has also been shown to be activated in BRAF inhbitor-resistant melanoma cells, which contributes to invasiveness[110,111].

The uPA/urokinase-type plasminogen activator receptor [uPAR] (plasminogen activation) system is a central regulator of angiogenesis and melanoma progression, significantly influencing cell migration, invasion, and metastasis[112,113]. Upregulation of the uPA gene is an early marker in melanocyte transformation with dysregulated enzymatic activity closely linked to malignancy. Unlike benign nevocytes, atypical nevocytes and melanoma cells have elevated levels of uPA and plasminogen activator inhibitor type 1 (PAI-1) mRNAs[114]. In addition, melanoma cells indirectly boost pro-angiogenic activity by releasing extracellular vesicles containing uPAR[84], establishing the uPA/uPAR system as a key contributor to melanoma angiogenesis (**Table 1**).

Microenvironment and immune modulation driving melanoma angiogenesis

Angiogenesis enables the formation of new blood vessels from pre-existing blood vessels through a series of regulated processes involving various factors with both pro- and anti-angiogenic roles[115]. Malignant cells can disrupt the physiologic balance in favor of vascular growth by recruiting and activating cells within the TME, thus triggering a phenomenon essential for cancer development and progression[116].

The TME, which consists of immune cells, stromal cells, blood vessels, and ECM, has a critical role in supporting cancer cell survival, invasion, and metastatic dissemination. Specifically, the TME promotes angiogenesis, oxygen and nutrient replenishment, and orchestrates blood vessel development, with vascular ECs, fibroblasts, and mast cells acting as key contributors[117].

During the early stages of tumor development, cancer cells rely on passive diffusion for gas and nutrient exchange. However, as tumors grow and reach 1–2 mm^3 in size, tumors experience hypoxia and acidity due to oxygen depletion and

waste accumulation. This hypoxic state activates HIFs, which in turn stimulate angiogenesis by promoting endothelial secretion of pro-angiogenic factors, like VEGF, PDGF, and EGF. Among these pro-angiogenic factors, VEGF has a central role by stimulating endothelial migration and lumen formation, followed by basement membrane deposition. Despite these pro-angiogenic mechanisms, tumor-associated blood vessels often remain immature and leaky. Furthermore, ECs undergo EndMT, which leads to differentiation into cancer-associated fibroblasts (CAFs), further contributing to tumor cell migration and invasion[117].

CAFs originate from multiple sources, including resident fibroblasts, bone marrow-derived mesenchymal stem cells, and ECs undergoing EndMT[118]. CAF activation is mediated by melanoma cells and various TME components, including cytokines, growth factors, and ECM proteins[118]. Once activated, CAFs significantly impact melanoma progression by remodeling the ECM through the secretion of collagen, fibronectin, and hyaluronic acid, thereby facilitating tumor invasion and metastasis. In addition, CAFs secrete growth factors, which further support melanoma cell proliferation, survival, and angiogenesis[119,120]. Moreover, CAFs contribute to therapy resistance by releasing factors that support tumor cell survival and modifying the ECM to limit drug penetration. In parallel, the secretion of cytokines and chemokines, including IL-1α, IL-1β, IL-6, IL-8, and CXCL10, and overexpression of PD-L1 further promotes melanoma invasion through complex molecular interactions[121].

CAFs also modulate immune responses by secreting immunosuppressive molecules, like IL-6, IL-10, and TGF-β, and by promoting recruitment of Tregs and myeloid-derived suppressor cells (MDSCs)[119,120].

In addition CAFs, another crucial immunosuppressive component of the TME is MDSCs, which not only enhance EC proliferation to stimulate angiogenesis but also promote melanoma cell proliferation and VM formation[122]. Furthermore, MDSCs inhibit T lymphocyte responses against tumors through various mechanisms[123].

Another important immune component linked to tumor angiogenesis is mast cells. Invasive melanomas exhibit a greater mast cell density than benign nevi and melanoma *in situ*[124]. A significant correlation has been noted between the microvessel count, FGF-2–positive tumor cells, mast cell density, melanoma progression, and poor prognosis[125,126]. Moreover, dermal mast cells immunoexpress VEGF in cutaneous malignant melanoma and mast cell density and microvascular density serve as prognostic markers. Elevated mast cell and microvascular density levels are associated with reduced patient survival[127].

Melanoma-associated macrophages (MaMs) also contribute significantly to TME modulation and melanoma progression. MaMs are highly plastic and adapt functional phenotypes in response to microenvironmental cues. MaMs primarily differentiate into two polarized states within melanoma: the classically activated M1 phenotype; and the alternatively activated M2 phenotype[128]. While M1 macrophages promote an anti-tumor immune response by releasing cytokines, such as IL-12 and TNF-α, which enhance cytotoxic T cell activity, M2 macrophages exhibit the opposite effect by facilitating tumor progression through immunosuppressive functions, including secretion of IL-10 and TGF-β, which promote angiogenesis, tissue remodeling, and immune evasion.

The intricate interplay between angiogenesis and immune regulation within the TME has direct implications for melanoma growth and response to immunotherapy. Indeed, studies analyzing angiogenic risk models and immune infiltration have revealed significant associations between angiogenesis-related genes and immune cells, such as memory B cells, activated memory CD4+ T cells, M1 macrophages, and gamma delta T cells[115]. Notably, CD4+ T cells directly eliminate tumor cells and the high infiltration levels correlate with improved responses to immunotherapy[129].

Similarly, tumor-infiltrating B cells contribute to the antitumor immune response, while tumor-infiltrating B cell deficiency has been associated with poorer outcomes in patients treated with ICIs[130,131].

Immune cell infiltration in cutaneous melanomas appears to be hampered by the limited adhesion of lymphocytes to newly formed blood vessels[132]. Leukocytes require the coordinated action of various molecules to reach the TME, including selectins, PECAM-1, intracellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2, respectively), and vascular cell adhesion molecule-1 (VCAM-1), which regulate rolling, adhesion, and subsequent migration[133]. Blood vessels in intratumoral cutaneous melanomas exhibit reduced expression of P-selectin, VCAM-1, E-selectin, and ICAM-1, unlike adjacent normal tissues where these molecules are normally expressed[134]. This downregulation of adhesion molecules may be attributed to VEGF overexpression[135].

Ultimately, melanomas, which are characterized by high angiogenesis, exhibit greater resistance to checkpoint inhibitors[136]. This feature is likely due to the interplay between

aberrant tumor angiogenesis and immunosuppression. The TME, often hypoxic and characterized by high interstitial fluid pressure, not only fosters immunosuppressive conditions but may also reduce the effectiveness of immunotherapy[137]. In addition, VEGF with other angiogenic factors has a pivotal role in modulating immune responses and promoting an immunosuppressive microenvironment.

VM in melanoma

VM in cancer

VM was first described to occur in patients with uveal melanoma in 1999, in which highly invasive tumor cells were shown to form alternative perfusion pathways independent of ECs. Maniotis et al. demonstrated periodic acid-Schiff (PAS)-positive vascular channels linked to red blood cell-containing spaces[23]. VM involves aggressive tumor cells adopting endothelial-like phenotypes, which contribute to vascularization without traditional angiogenesis. This phenomenon correlates with poor prognosis and metastatic potential, possibly facilitating tumor perfusion and dissemination[23,138]. PAS- and laminin-positive networks connect VM structures with endothelial vessels in aggressive melanomas, suggesting para-circulation independent of angiogenesis. Orthotopic mouse models of human uveal melanoma revealed ECM-based networks conducting fluid that correlate with PAS-positive structures[138]. These findings imply embryonic vasculogenesis-like processes because gene expression in VM-capable melanomas includes markers of epithelial, endothelial, and fibroblast phenotypes[139,140]. Although the molecular mechanisms driving VM formation are not fully understood, it is now clear that VE-cadherin is pivotal for VM[26].

VE-cadherin and VEGF receptors in VM regulation

VE-cadherin is a transmembrane protein typically situated in ECs, where VE-cadherin has a crucial role in cell-cell adhesion[141]. While specific to ECs under normal conditions, Expression of VE-cadherin in melanoma enhances tumor aggressiveness. Loss of VE-cadherin abolishes VM formation, as demonstrated by Hendrix et al.[142,143]. The interaction of VE-cadherin with signaling pathways, like Nodal/Notch, PI3K, and MAPK, underscores the VE-cadherin regulatory role[144,145]. VE-cadherin function in VM is regulated by VEGFRs, particularly VEGFR-2 and -1. VEGFR-2, which is highly expressed in ECs, facilitates the formation of primitive tubular vessels, while VEGFR-1 is also implicated in VM in melanoma cells. VEGF-A activates these receptors, promoting vascular permeability and endothelial growth by disrupting adherens and tight junctions, which are mediated *via* VE-cadherin phosphorylation. This phosphorylation enhances VE-cadherin interactions with proteins, such as β-catenin and plakoglobin, and p120 *via* an Src-dependent mechanism[26,146], which weakens endothelial barriers and facilitating tumor dissemination[26,27,34,147-151]. EC adhesion is a tightly regulated process in which VE-cadherin plays a pivotal role in the formation and stabilization of adherens junctions. This transmembrane protein interacts through the cytoplasmic tail with the armadillo family members, p120-catenin, β-catenin, and plakoglobin. Notably, β-catenin binds to α-catenin, which links the cadherin complex to the actin cytoskeleton, thereby maintaining endothelial cohesion and barrier integrity[146].

Phosphorylation of VE-cadherin induced by Src kinase upon VEGF-A stimulation disrupts binding to p120 and β-catenin. This modification increases vascular permeability and contributes to junctional destabilization. p120 is essential for stabilizing VE-cadherin at the plasma membrane and preventing VE-cadherin endocytosis under physiologic conditions. Depletion of p120 leads to widespread loss of cadherins and complete disassembly of cell-cell junctions[146].

VEGF-A is known to promote vascular permeability by disrupting adherens and tight junctions. VEGF-A enhances VE-cadherin phosphorylation and internalization through an Src-dependent pathway, ultimately leading to the destabilization of endothelial contacts[26].

A delicate balance between the VE-cadherin/VEGFR-2 complex and VEGF signaling is crucial for maintaining endothelial barrier integrity. VE-cadherin physically interacts with VEGFR-2 in quiescent ECs, preventing VE-cadherin endocytosis and maintaining VE-cadherin localization at the cell membrane. However, this association is disrupted upon VEGF stimulation, promoting phosphorylation and internalization of both proteins into separate intracellular compartments. Excessive VEGF levels can overcome the protective effect of VE-cadherin on VEGFR-2, thus facilitating tumor cell extravasation and metastatic dissemination, especially in pathologic settings, such as cancer[26,146,152].

A study conducted involving uveal melanoma further clarified the involvement of VEGF-R2 in VM, focusing on

the co-receptor, CD146[153], which contributes to VM *via* the p38/AKT/NF-Kb signaling pathway[154]. CD146 is significantly upregulated in metastatic uveal melanoma[155] and is co-localized with the VM structure stained by PAS[156]. CD146 modulates vasculogenic formation by regulating VE-cadherin and FAK phosphorylation, which are critical for VM. CD146 knockdown impairs these processes, confirming a central role in VM[153,157].

VEGFR-1 promotes VM through PI3K/PKC signaling and supports VE-cadherin expression[24,26]. Pigment epithelium-derived factor (PEDF) inhibits VEGF-A/VEGFR-1 signaling, reducing melanoma aggressiveness and VM formation[24,158]. VEGF-A promotes vascular maturation by recruiting pericytes through PDGF-BB. Elevated PDGF-BB expression is associated with VM-positive tumors. Dual inhibition of VEGF-A and PDGF-BB reduces cell proliferation, invasion, and VM markers, including VE-cadherin and EphA2. This combined strategy significantly affects VM pathways, highlighting the therapeutic potential[159,160].

EphA2 in VM formation

EphA2, a tyrosine kinase receptor, is linked to VM and EphA2 activity and phosphorylation depend on an interaction with ephrin-A1, although EphA2 can be constitutively active in some tumor cells. Like VE-cadherin, EphA2 is only expressed in highly aggressive tumors[161]. VE-cadherin and EphA2 are co-localized on the plasma membrane in VM, particularly at cell-cell contact sites. The removal of VE-cadherin causes a redistribution of EphA2 to the cytoplasm and a reduction in EphA2 phosphorylation. These data suggest that VE-cadherin may facilitate translocation of EphA2 to the plasma membrane[162,163]. In addition, overexpression of EphA2 increases MMP-2 levels in a FAK-dependent manner[164]. FAK is strongly phosphorylated in aggressive melanomas but not in less aggressive melanomas. EphA2 promotes VM formation through a signaling cascade involving FAK and ERK, intersecting the PI3K pathway at the activation of MMP-14[24,165]. PI3K regulates the activity and expression of MMP-14 in highly aggressive tumor cells. MMP-14, in turn, activates MMP-2, which cleaves laminin, producing fragments (γ2′ and γ2x) that are secreted into the ECM, facilitating tumor cell migration[143,166] (**Figure 2**). It has long been demonstrated that cooperation between laminin, MMP2, and MMP-14 is essential for VM of melanoma cells. Similarly, downregulation of EphA2, laminin, and VE-cadherin expression results in a complete inability of these cells to form VM in 3D cultures[26,143].

Hypoxia as a driver of VM

Oxygen deficiency in tumor growth is crucial for survival and malignancy. HIFs and hypoxia-responsive elements (HREs) stabilize hypoxia and regulate gene expression. HIFs stabilize under hypoxic conditions, activating genes involved in tumor cell adaptation, such as VEGF-A, VEGFR-1, EphA2, Twist, Nodal, COX-2, and VE-cadherin, all linked to the process of VM[24,167]. Specifically, VE-cadherin possesses up to six HREs upstream of the promoter[168].

As a result, hypoxia has been shown to stimulate VM in many tumor cell lines[169-171]. VM formation is significantly increased in murine melanoma models under ischemic conditions. Moreover, a positive correlation has been found between HIF-1α and VEGF expression in ischemic tumor cells[172]. Hypoxia induces elevated expression of the anti-apoptotic protein, Bcl-2, in human melanoma, which subsequently stimulates VE-cadherin expression[144]. In summary, hypoxia is a key factor in signaling pathways involved in VM. Hypoxia can also influence VM through BNIP3, a member of the Bcl-2 family, which is highly upregulated under hypoxic conditions and contributes to cell migration and VM development in melanoma. BNIP3 facilitates these processes by altering actin cytoskeleton organization, while BNIP3 inhibition completely blocks VM, altering cell size and shape and causing the formation of actin stress fibers that reduce tight and adherens junctions[173].

Hypoxia drives lymph node metastasis in melanoma through upregulation of uPAR[174]. Among Bcl-2 family proteins, Bcl2L10, which is highly expressed in melanoma cell lines and patient samples, has a pivotal role in VM. Genetic and pharmacologic inhibition of uPAR impairs Bcl2L10-dependent VM, emphasizing the critical role of uPAR[175,176]. Similarly, Bcl-xL induces VM in *in vitro* and *in vivo* melanoma models, highlighting the importance of Bcl-2 proteins in invasion and VM[176].

Plasminogen activator system and VM

The plasminogen activator system, including uPA and uPAR, is strongly correlated with melanoma metastasis and aggressiveness and is highly expressed in advanced melanoma. Downregulation of uPAR reduces melanoma cell

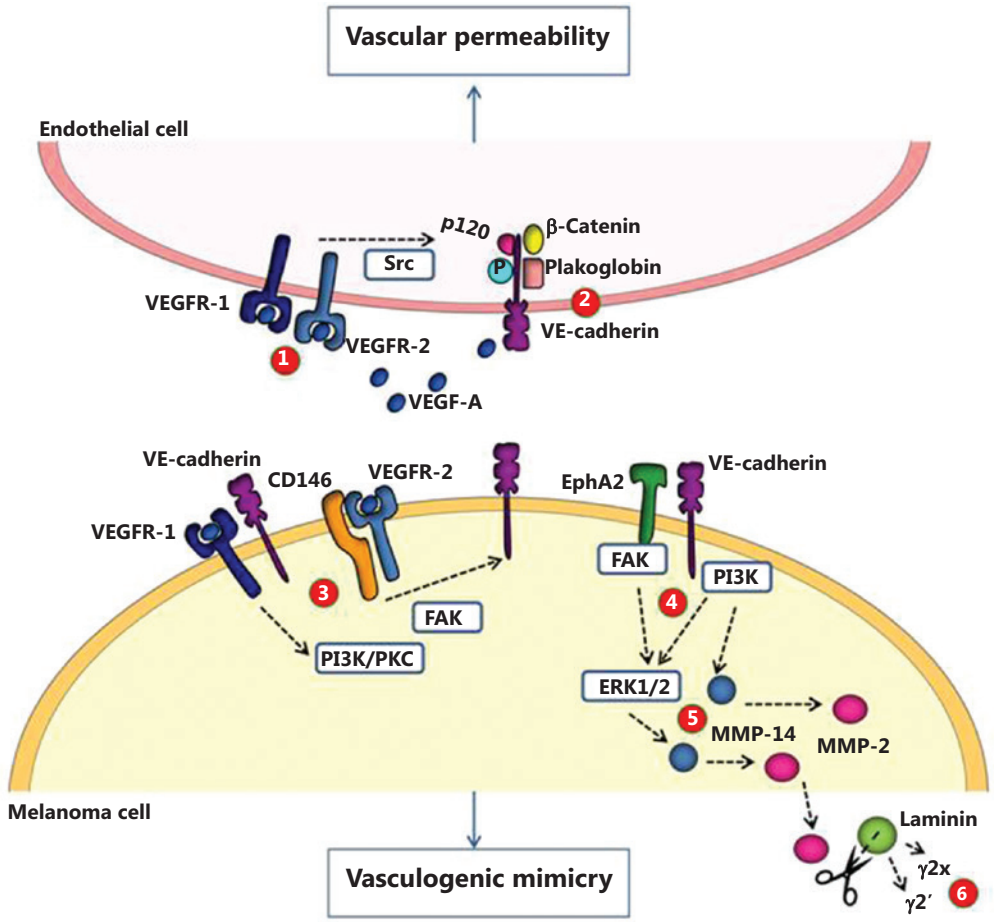

Figure 2 Molecular mechanisms underlying vascular permeability and VM in melanoma-endothelial cell interactions: The diagram illustrates the key molecular signaling pathways and protein interactions involved in VM and vascular permeability. VEGF-A activates VEGFR-1 and VEGFR-2 in ECs (1) and induces tyrosine phosphorylation of VE-cadherin and modulates the association with interacting partners, such as β-catenin, plakoglobin, and p120, *via* an Src-dependent mechanism and enhances vascular permeability by destabilizing adherens and tight junctions, leading to a transient opening of the endothelial cell-cell contacts (2). VE-cadherin can be regulated in melanoma cells by CD146 and the coreceptor, VEGFR-2, through the FAK signaling pathway. The expression is further supported by VEGFR-1, which mediates VM *via* the PI3K/PKC pathway (3). EphA2 interacts with FAK. The signaling pathways activated by both EphA2 and VE-cadherin converge to stimulate PI3K (4). PI3K positively regulates both the activity and expression of MMP-14 in tumor cells. FAK and PI3K contribute to increased activation of ERK1/2, overexpression of MMP-14, and enhanced MMP-2 activity (5). Both MMP-14 and MMP-2 promote the cleavage of the γ2 chain of laminin into promigratory fragments (γ2′ and γ2x) (6). Release of these fragments (acting as molecular signals) into the tumor microenvironment can enhance the migration, invasion, and ultimately the vasculogenic mimicry of aggressive melanoma tumor cells. The figure was partly generated using Servier Medical Art, provided by Servier and licensed under a Creative Commons Attribution 3.0 unported license (https://smart.servier.com/). EphA2, Eph receptor A2; MMP-2, matrix metalloproteinase 2; MMP-14, matrix metalloproteinase 14; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

migration, invasion, and VM in 2D and 3D cultures[176]. Moreover, uPAR inhibition disrupts VM and capillary formation in drug-resistant melanoma cells using RNA interference or peptides, like M25, underscoring the potential of uPAR as a therapeutic target[177]. Overall, the interplay between hypoxia, Bcl-2 proteins, and uPAR establishes a network critical for VM, metastasis, and melanoma progression.

Role of the TME in VM: molecular mechanisms and immune modulation

The TME has been hypothesized to have a pivotal role in cancer development and progression, especially in invasion and metastatic processes[178,179]. The TME encompasses a complex physicochemical milieu, including stromal cells,

fibroblasts, blood vessels, oxygen levels, immune cells, the ECM, and cytokines[180]. A reciprocal interaction exists between the TME and the tumor that significantly influences tumor progression, including VM. The first evidence linking the TME to VM was reported by Hendrix et al. in 2002[181]. Hendrix et al. inoculated human melanoma cells of varying aggressiveness using an ischemic model created by femoral artery ligation in nude mice. Hendrix et al. concluded that only highly aggressive melanoma cells exhibited overlap with ECs during vasculogenesis in ischemic muscle. Immunohistochemistry analysis further identified robust expression of Notch-3 and -4 exclusively in highly aggressive melanoma cells but absent in control cells[181]. In a subsequent study, Hendrix et al. reported that aggressive melanoma cells can modify the ECM and reprogram less aggressive cells to induce VM[181]. Microarray analysis confirmed differential gene expression in less aggressive melanoma cells pre-conditioned by the microenvironment of aggressive cells. The analysis identified upregulation of key genes, including *EphA2*, *VE-cadherin*, *TIE-1*, *VEGF-C*, MMPs, and the γ2 chain of laminin 5 (Ln5γ2)[182].

Among the various factors involved in VM, CD248, a type I transmembrane protein primarily expressed in stromal cells, facilitates interactions with ECM proteins and is linked to MM (**Figure 3A**). Indeed, CD248 is present in 85% of the TMEs in MM vascularization but not in normal tissues, suggesting a role for CD248 in melanoma progression[183,184].

Kuo et al. reported that CD248 expression in melanoma tumor cells correlates with fibronectin interaction, FAK activation, MMP-9 expression, and increased cell migration. Tumor cells with autonomous CD248 expression exhibit the potential to form VM, thereby supporting tumor vascularization and promoting growth and metastasis. These findings indicated that CD248 contributes to tumor malignancy and highlights the potential of CD248 as a target for therapeutic intervention[183].

Moreover, some studies suggest that the expression of adhesion molecules, such as PECAM-1, on vessels formed through VM[185] may facilitate the interaction between circulating leukocytes and newly formed vessels, indicating that the tumor might actively modulate the TME by recruiting specific immune cells[132].

In the context of VM, tumor cells or other tumor-associated cells can form endothelial-like structures, supplying oxygen and nutrients to the tumor while also providing a potential escape route from immune surveillance[186].

Despite these insights, the role of lymphocytes in the modulation of VM, as well as angiogenesis, has not been fully elucidated. Overall, the impact of lymphocytes on VM depends on the type, quantity, and activation status within the TME. However, it is known that activated CD4+ T cells release various cytokines and signaling molecules, such as IL-2 and IFN-γ, thereby inhibiting VM formation. Similarly, CD8+ T cells and natural killer (NK) cells can directly kill tumor cells[187].

In addition to these cell populations, Tregs have a crucial role in regulating immune tolerance and suppressing immune responses. Indeed, elevated levels of Tregs promote tumor growth by inhibiting the activity of CD4+ and CD8+ T cells[188], thus contributing to VM formation.

In parallel, tumor-associated macrophages (TAMs) also have an immunomodulatory role that can influence VM because TAMs secrete various growth factors and cytokines, including VEGF, TGF-β, FGF, supporting angiogenic processes and promoting VM occurrence[189]. Specifically, TAMs mediate stromal remodeling by secreting MMPs that alter ECM integrity. These modifications in the TME facilitate VM formation[189].

Furthermore, TAMs can induce epithelial–mesenchymal transition (EMT) in tumor cells by secreting factors, such as TGF-β, IL-6, and IL-10, which concurrently exert immunosuppressive effects[190]. The influence of TAMs may impair the efficiency of immune cells, reducing the ability to recognize and eliminate tumor cells effectively, thus inducing microenvironmental changes favorable to VM development.

Taken together, these findings highlight an important consideration. Specifically, immune function regulation may represent a crucial strategy in cancer treatment influencing VM and tumor progression.

Cancer stem cells (CSCs) and VM adaptation

The VM process relies on the adaptive response and plasticity of tumor cells, a characteristic prominently associated with CSCs. CSCs, a highly plastic subpopulation, possess the capacity to transdifferentiate into various cell types, including ECs, which contribute to tumor vascularization[191,192]. This plasticity is particularly evident in the perivascular niche and correlates with increased tumor aggressiveness[193,194]. CSCs, which are characterized by markers in melanoma, such as ATP-binding cassette subfamily B member 5 (ABCB5) and CD133, have pivotal roles in tumor progression and VM[195-197] (**Figure 3B**).

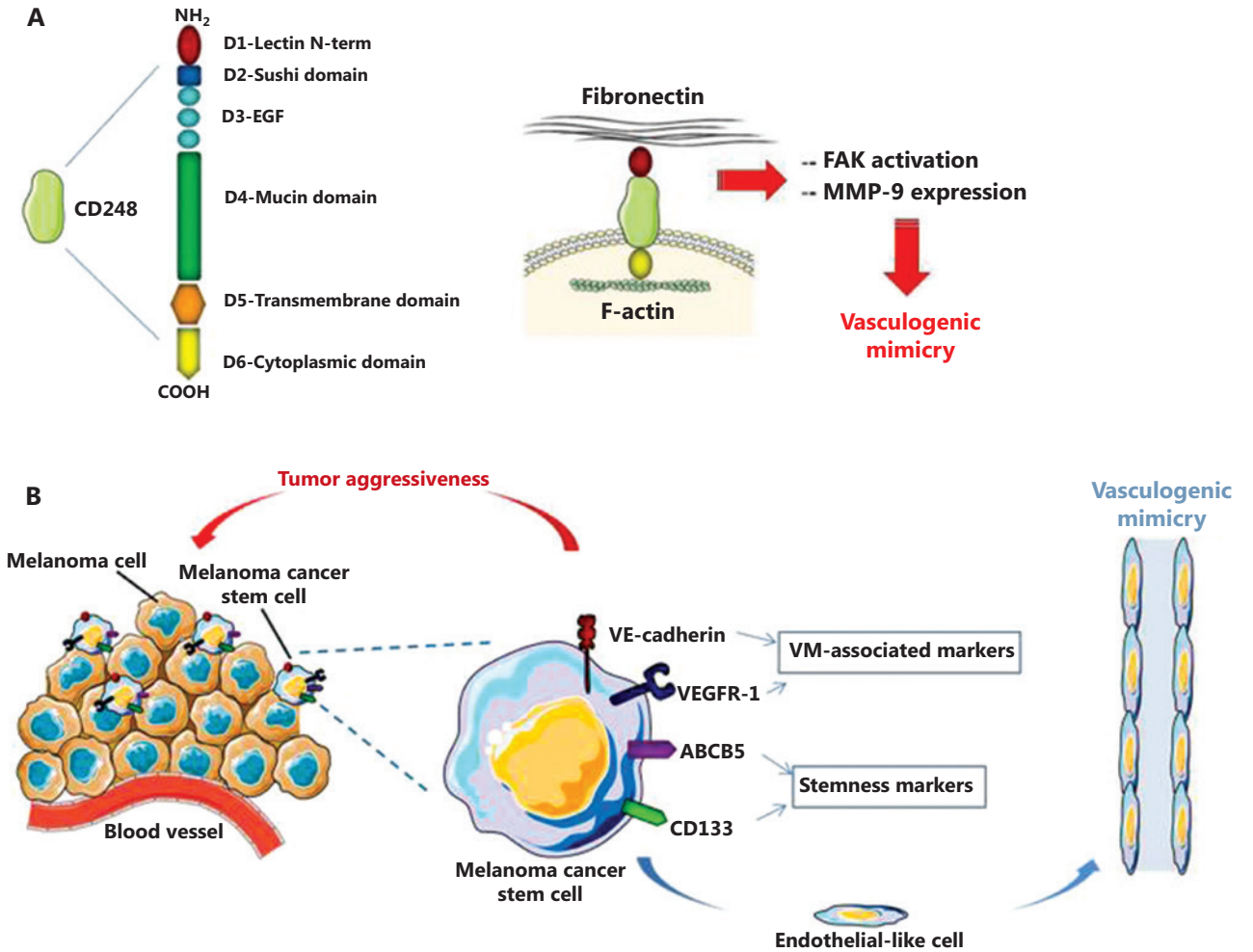

Figure 3 Molecular markers associated with vascular mimicry and cellular stemness. (A) Structural domains of CD248 and their role in promoting VM: The N-terminal lectin domain of CD248 may enhance tumor cell adhesion to fibronectin, while the C-terminal cytoplasmic domain can anchor to F-actin, thereby establishing a connection between F-actin filaments. CD248 interacts with fibronectin, leading to FAK activation and MMP-9 expression, which are critical processes for actin cytoskeleton remodeling and VM formation. (B) Melanoma cancer stem cells (MCSCs): MCSCs exhibit high plasticity and contribute to VM formation. These cells express key VM-associated markers and stemness, including VE-cadherin and VEGFR-1, and ABCB5 and CD133, respectively. MCSCs transdifferentiate into endothelial-like cells, promoting VM and enhance melanoma aggressiveness. This schematic figure was partly generated using Servier Medical Art, provided by Servier and licensed under a Creative Commons Attribution 3.0 unported license (https://smart.servier.com/). ABCB5, ATP-binding cassette subfamily B member 5; MMP-9, matrix metalloproteinase 9; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

VM-forming tumor cells exhibit stem cell-like plasticity and an undifferentiated biomolecular architecture reminiscent of embryonic cells, linking CSCs to VM across cancers, including melanoma and breast cancer[158]. Key intracellular pathways implicated in VM include the PI3K-Akt-PTEN axis, which activates MMP-14, MMP-2, and processes laminin isoforms essential for VM formation[158,198]. Melanoma CSCs (MCSCs) express VE-cadherin and VEGFR-1, which are critical for VE-cadherin-dependent VM and tumor growth. Anti-VEGF-A therapies have shown limited success, as melanomas can adapt to VEGF-A blockade by adopting VM as an alternative angiogenic mechanism, enriched by a HIF1α-dependent process[27,199]. CSCs also facilitate metastasis through EMT, enhancing migration, invasiveness, and proliferation, even in harsh microenvironments. EMT and stemness-associated transcription patterns overlap with genes linked to VM, further underscoring the connection between CSCs, VM, and drug resistance[143,200,201]. A subset of metastatic

CSCs disseminates to distant sites, initiating tumor growth, underscoring the challenges posed by CSC heterogeneity and plasticity in anti-metastatic therapies[202]. Aggressive melanoma cells exhibit de-differentiation with downregulation of melanoma-specific markers and upregulation of genes linked to various cellular phenotypes and vascular formation, complicating histopathologic identification and therapeutic targeting[143]. Research continues to investigate VM molecular mechanisms and therapeutic implications, particularly given the inefficacy of conventional anti-angiogenic treatments against these structures.

Advances in anti-angiogenic therapy for melanoma

Recent research has shown that inhibiting angiogenesis may enhance the sensitivity of some cancers, including melanoma, to chemotherapy and radiation therapy[203]. Early-stage melanoma is typically managed through surgical excision, while advanced stages are treated with immunotherapy and targeted therapies, such as anti-angiogenic agents.

Angiogenesis research has identified numerous regulatory mechanisms, yet much of the focus remains on the VEGF-A/VEGFR signaling pathway due to the central role of the VEGF-A/VEGFR signaling pathway. US Food and Drug Administration (FDA)/European Medicines Agency (EMA)-approved angiogenesis inhibitors currently in clinical use include monoclonal antibodies (mAbs), aptamers, recombinant fusion proteins, immunosuppressants, and small-molecule tyrosine kinase inhibitors (TKIs). Prominent mAbs targeting VEGF-Ak include bevacizumab and ranibizumab. Bevacizumab is approved for various cancers, such as metastatic colorectal cancer (CRC), advanced/metastatic non-squamous non-small cell lung cancer, metastatic renal cell carcinoma (RCC), advanced/recurrent ovarian cancer, breast cancer (EMA only), recurrent glioblastoma multiforme (FDA only), unresectable/metastatic hepatocellular carcinoma, and metastatic cervical cancer. Several clinical trials have been conducted involving bevacizumab, both as monotherapy and in combination (www.clinicaltrials.gov), but it has not been approved for the treatment of this disease by international agencies, such as the FDA or EMA. Combination studies (NCT06163820 and NCT04356729) are ongoing, primarily to evaluate the therapeutic response when used in conjunction with immunotherapy (anti-PD1, anti-PD-L1, and anti-CTLA4). Ranibizumab, in contrast, is primarily used for ocular conditions, such as wet age-related macular degeneration, diabetic macular edema, macular edema following retinal vein occlusion, diabetic retinopathy, and myopic choroidal neovascularization. Several bevacizumab biosimilars have recently received market authorization by the FDA and EMA for cancer treatment.

Bevacizumab is pivotal in inhibiting VEGF-A binding to VEGFRs in metastatic melanoma treatment, thereby preventing EC proliferation and angiogenesis. A meta-analysis of randomized controlled trials and non-comparative c linical studies assessed the efficacy and safety of bevacizumab in combination with chemotherapy, targeted therapies, and interferon-γ for melanoma patients; the analysis revealed an overall response rate of 15.8%. Bevacizumab combined with carboplatin/paclitaxel significantly improving overall survival compared to carboplatin/paclitaxel alone. Common adverse effects included fatigue, nausea, leukopenia, thrombocytopenia, and neutropenia with hypertension reported in 32.4% of patients across all bevacizumab treatment regimens[204].

Additional mAbs include ramucirumab and olaratumab, which target VEGFR-2 and PDGFRα receptors, respectively. Ramucirumab has been approved for treatment of advanced/metastatic non-small cell lung cancer, advanced gastric cancer, gastroesophageal junction adenocarcinoma, advanced/unresectable hepatocellular carcinoma, and metastatic CRC, while olaratumab is approved for advanced soft tissue sarcoma[205]. In chemotherapy-naïve patients with MM, ramucirumab has been used alone or in combination with dacarbazine, yielding median progression-free survival rates of 2.6 months for combination therapy and 1.7 months for ramucirumab alone with an acceptable safety profile (NCT00533702)[206]. Conversely, no data are available for olaratumab in MM.

Among the oligonucleotide derivatives used as anti-angiogenic drugs, only pegaptanib has received FDA approval (specifically, for the treatment of wet age-related macular degeneration). Pegaptanib selectively binds to VEGF-A165[206]. However, pegaptanib has never been used in the treatment of cancer patients.

Another class of anti-angiogenic drugs includes recombinant fusion proteins, such as aflibercept and ziv-aflibercept, which are comprised of an IgG1 Fc region and VEGFR-1/-2 extracellular domains, thus targeting VEGF-A/B and PIGF. Known as "VEGF-A traps," these chimeric molecules have a high affinity for VEGF-A, blocking the interaction with VEGFR1/2[207,208]. Aflibercept and ziv-aflibercept are used in the treatment of ocular diseases (i.e., wet age-related macular degeneration,

diabetic macular edema, macular edema following retinal vein occlusion, diabetic retinopathy, and myopic choroidal neovascularization) and CRC, respectively[206]. In a study with 10 advanced melanoma patients resistant to anti-PD-1 therapy, a combination of ziv-aflibercept and pembrolizumab led to a partial response in 2 patients with mucosal melanoma and stable disease in 2 patients with ocular melanoma[209]. The immunosuppressants, thalidomide and lenalidomide, are also used as anti-angiogenic drugs, targeting VEGF-A, TNF, and NF-kB. Thalidomide and lenalidomide have received FDA approval for the treatment of multiple myeloma and mantle cell lymphoma (VEGFR-1/-2/-3, c-Kit, Flt-3, PDGFR-β, Raf, and Ret). There are no reports on use of thalidomide and lenalidomide in patients with melanoma.

The last class of anti-angiogenic drugs, the small molecule TKIs, include several agents that inhibit VEGFR-1/-2/-3, c-Kit, Flt-3, PDGFR-β, Raf, or Ret, such as sorafenib, sunitinib, pazopanib, vandetanib, regorafenib, and lenvatinib. In recent years, tyrosine kinase enzymes have been identified as critical targets in the treatment of melanoma[210-212] due to involvement in tumorigenesis and progression. TKIs aim to inhibit the catalytic function of kinases, thereby blocking the downstream signaling cascade activation[213,214]. Among the TKIs, sorafenib, sunitinib, and lenvatinib have been utilized for the treatment of melanoma patients. Sorafenib exerts a dual antitumor effect[215] because sorafenib not only directly inhibits tumor cell proliferation through mediation of the RAF/MEK/ERK pathway but also impairs tumor cell nourishment by inhibiting the formation of new blood vessels. This effect is achieved through inhibition of tyrosine kinase activity in VEGFR2, VEGFR3, PDGF-β, KIT, and FLT-3 receptors[170]. Sorafenib has been utilized in several clinical trials involving uveal melanoma patients but sorafenib was shown to have limited potential clinical benefits, as in NCT02517736[216]. Lenvatinib, another oral multi-TKI, exhibits effects on VEGFR1-3, FGFR1-4, PDGFR, and KI[171]. Additionally, lenvatinib inhibits the proliferation of human umbilical vein ECs and tubular formation to reduce tumor growth[217,218]. The safety and clinical efficacy of lenvatinib were evaluated in 77 patients with melanoma in a phase I study[219], which showed a partial clinical response rate of 15.6% with dose-limiting toxicities[219]. Furthermore, a decrease in the Ang-1 levels, which stimulates vessel maturation by acting on the TIE2 receptor, was considered an important factor associated with prolonged progression-free survival in patients with melanoma. Lenvatinib is also utilized in combination with the anti-PD-1 mAb, pembrolizumab, for MM patients with brain metastases [NCT04955743], the results of which are not available. Finally, sunitinib, an oral multi-TKI, has been approved for therapeutic use in RCC, gastrointestinal stromal tumors, and pancreatic neuroendocrine tumors. Sunitinib primarily targets VEGFRs, KIT, and other receptors in melanoma. Sunitinib has been evaluated in multiple clinical trials assessing its safety and efficacy, including NCT00462982 for patients with melanoma-related brain metastases; NCT01005472, NCT00304200, and NCT00496223 in combination with temozolomide or dacarbazine; NCT01216657 for patients with chemo-refractory metastatic melanoma; and NCT02400385 and NCT00631618 for the treatment of melanoma with KIT mutations. Additionally, sunitinib has been investigated in patients with uveal melanoma to assess the potential in preventing the spread of cancer to other parts of the body, as registered on ClinicalTrials.gov, but sunitinib did not have significant clinical activity in such patients. However, sunitinib has not been approved by the FDA for use in melanoma patients but remains under investigation for this indication.

Emerging anti-angiogenic agents and natural compounds

Although multiple therapeutic options for treating melanoma are currently available, such as surgical removal, chemotherapy, and immunotherapy, the prognosis for advanced melanoma remains poor[7-9]. Therefore, finding new agents for treating advanced melanoma is needed. Among other molecules of endogenous origin or from fruits and vegetables that have shown effectiveness in the melanoma model, endostatin, betulinic acid, apigenin, and jatrorrhizine hydrochloride have been evaluated. Endostatin is a 20 kDa C-terminal fragment derived from collagen type XVIII[220]. Endostatin is a potent endogenous inhibitor of angiogenesis. In 2005 endostatin was approved by the Chinese FDA for treatment of non-small cell lung cancer[221,222]. However, the clinical efficacy of endostatin remains controversial and requires further investigation in the treatment of patients with MM. The combination of recombinant human endostatin (Rh-endostatin) and chemotherapy (NCT03095079) has shown good tolerability and a manageable toxicity profile[223]. Recently, endostatin has been identified as a prognostic biomarker for patients with MM [224]. Several studies have demonstrated that endostatin levels are closely associated with aggressive phenotypes or poor outcomes in various malignancies, including MM. A phase IV study indicated that

endostatin influences melanoma invasion by regulating T cell activation[224].

In recent years antitumor compounds derived from traditional Chinese medicine have become a focus of research. Betulinic acid, extracted from plane and birch trees, has anti-angiogenic effects in melanoma. One study reported that betulinic acid exhibits inhibitory effects on A375 melanoma cells through mitochondrial apoptosis and the glycolysis pathway[225]. Apigenin, a flavonoid naturally present in fruits and vegetables, may inhibit melanoma cell proliferation and angiogenesis by suppressing TNF-α secretion and affecting the PI3K/Akt/mTOR signaling pathway[226,227]. Jatrorrhizine hydrochloride, a component of *Coptis chinensis*, exhibits anti-metastatic and anti-proliferative effects on human C8161 melanoma cells. Mechanistic studies have shown that JH induces G0/G1 cell cycle arrest in C8161 tumor cells. Moreover, JH reduces neovascularization in C8161 cells and interferes with the expression of VE-cadherin, the main endothelial adhesion molecule controlling cell junctions and blood vessel formation, suggesting that JH could be a novel potential anti-melanoma drug candidate[228].

The abovementioned drugs reported are summarized in **Table 2**.

Targeting VM: emerging therapeutic approaches

Starting from the analysis of the molecular pathways involved in VM, new therapeutic targets have been identified, emphasizing the importance of addressing tumor heterogeneity and the complexity of blood vessel networks. Hypoxia, whether induced by rapid tumor growth or traditional therapies, has been shown to promote VM, suggesting the potential of targeting specific cell populations with agents that possess anti-VM activity. Several pathways have critical roles in this

Table 2 Clinical and preclinical studies of anti-angiogenic therapies in metastatic and uveal melanoma

Disease	Drug	NCT number	Phase	Status	Safety/Adverse events (AEs)	Reference
MM	Bevacizumab plus ipilimumab and nivolumab	NCT06163820	1/2	Not yet recruiting		
MM	Bevacizumab plus atezolizumab	NCT04356729	2	Recruiting		
MM	Pembrolizumab plus bevacizumab	NCT02681549	2	Active, not recruiting	10.8% grade 3 AEs for bevacizumab and 18.9% for pembrolizumab	229
	Bevacizumab and atezolizumab with or without cobimetinib	NCT03175432	2	Active, not recruiting	No results posted	230
MM	Ramucirumab plus dacarbazine	NCT00533702	2	Completed	The AEs are generally safe and well-tolerated.	206
MM	Ziv-aflibercept plus pembrolizumab	NCT02298959	1b	Active, not recruiting	No results posted	209
UM	Sorafenib	NCT02517736	2	Completed	No results posted	216
MM	Lenvatinib plus pembrolizumab	NCT04955743	1	Recruiting		219
UM	Sunitinib	NCT01551459	2	Completed	No results posted	231
MM	Endostatin plus dacarbazine and cisplatin	NCT03095079	2	Unknown status		232
MM	Betulinic acid	Preclinical				225
MM	Apigenin	Preclinical				216,217
MM	Jatrorrhizine hydrochloride	Preclinical				228

MM, metastatic melanoma; UM, uveal melanoma; NCT numbers, clinical trial identifiers.

process, including VE-cadherin, Ras, HER2, VEGF-A, COX-2, autophagy, and the Nodal/Smad signaling cascade.

It is clear that drugs targeting these pathways, particularly anti-angiogenic agents, have demonstrated limited therapeutic efficacy in clinical settings[233]. However, one compound (CVM-1118) has recently shown a significant anti-VM effect. CVM-1118 was reported to have potent activity in progressive, unresectable advanced hepatocellular carcinoma when administered in combination with nivolumab at the 2024 ASCO meeting. This regimen not only demonstrated strong anti-VM effects but also a favorable safety profile, making CVM-1118 a superior option compared to the standard combination (bevacizumab and atezolizumab) for these patients[234].

Other compounds under investigation for anti-VM potential include PF-562271, AKB-9778, and imatinib mesylate (STI-571)[235]. PF-562271, a focal adhesion kinase (FAK) inhibitor, disrupts VM by dissociating β-catenin from VE-cadherin, resulting in the downregulation of *c-Myc* and *Twist-1*, both of which are transcription factor (TCF)-4-dependent genes[151]. Similarly, AKB-9778, an inhibitor of vascular endothelial protein tyrosine phosphatase (VE-PTP), interferes with the maturation of tumor vessels by deactivating the endothelial TIE-2 receptor, tyrosine kinase[236]. Imatinib mesylate, a potent VM inhibitor, reduces pericyte numbers and blocks PDGFRs, thereby preventing the formation of vascular-like networks[159]. Currently, studies (NCT00027586 and NCT00074308) have been completed, in which imatinib mesylate was administered alone or in combination with bevacizumab, achieving minimal clinical efficacy and no significant clinical activity, respectively[237,238]. However, the authors concluded that the potential benefit in patients with specific c-kit alterations warrants further investigation and that future success will depend on better patient selection and combination therapies. Furthermore, imatinib mesylate is undergoing clinical trials for MM in combination with immunotherapy or targeted therapies, such as pembrolizumab or binimetinib.

In addition to these strategies, novel approaches are emerging that aim to inhibit VM while simultaneously enhancing the efficacy of immunotherapy. Doxycycline, for example, has been shown to have significant anti-VM activity *in vivo* in melanoma models, particularly when combined with anti-PD-1 therapy. This combination not only inhibits VM but also reduces MDSCs, indicating a promising role as an immunotherapy enhancer. Such findings suggest new therapeutic applications for this well-established antibiotic[58].

The use of anti-VM therapies is also being explored in uveal melanoma, a highly metastatic eye cancer. Artesunate has demonstrated potent anti-VM effects by modulating pathways involved in neoangiogenesis, particularly those regulated by HIF-1α. By targeting HIF-1α, artesunate influences downstream factors, such as PDGF-BB and VEGF-AA, which are hyperactivated under hypoxic conditions. In addition, artesunate inhibits VEGFR-2, PDGFR, and VM-related proteins, like EphA-2 and VE-cadherin, highlighting the potential as an effective anti-VM agent in this context[58,239].

The abovementioned drugs are summarized in **Table 3**.

Table 3 Clinical and preclinical studies targeting vasculogenic mimicry in metastatic and uveal melanoma

Disease	Drug	NCT number	Phase	Status	Safety/adverse events (AEs)	Reference
MM	CVM-1118	Preclinical				240
MM	PF-562271	Preclinical				151
MM	AKB-9778	Preclinical				236
MM	STI-571	NCT00027586	2	Completed	Grade 3 or 4 AEs: fatigue and edema (>10%)	237
MM	STI-571 plus bevacizumab	NCT00074308	1/2	Completed	Well-tolerated	238
MM	STI-571 plus pembrolizumab	NCT04546074	1/2	Recruiting		241
MM	STI-571 plus binimetinib	NCT04598009	2	Recruiting		242
MM	Doxycycline plus immunotherapy	Preclinical				58
UM	Artesunate	Preclinical				58,228

MM, metastatic melanoma; UM, uveal melanoma; NCT numbers, clinical trial identifiers.

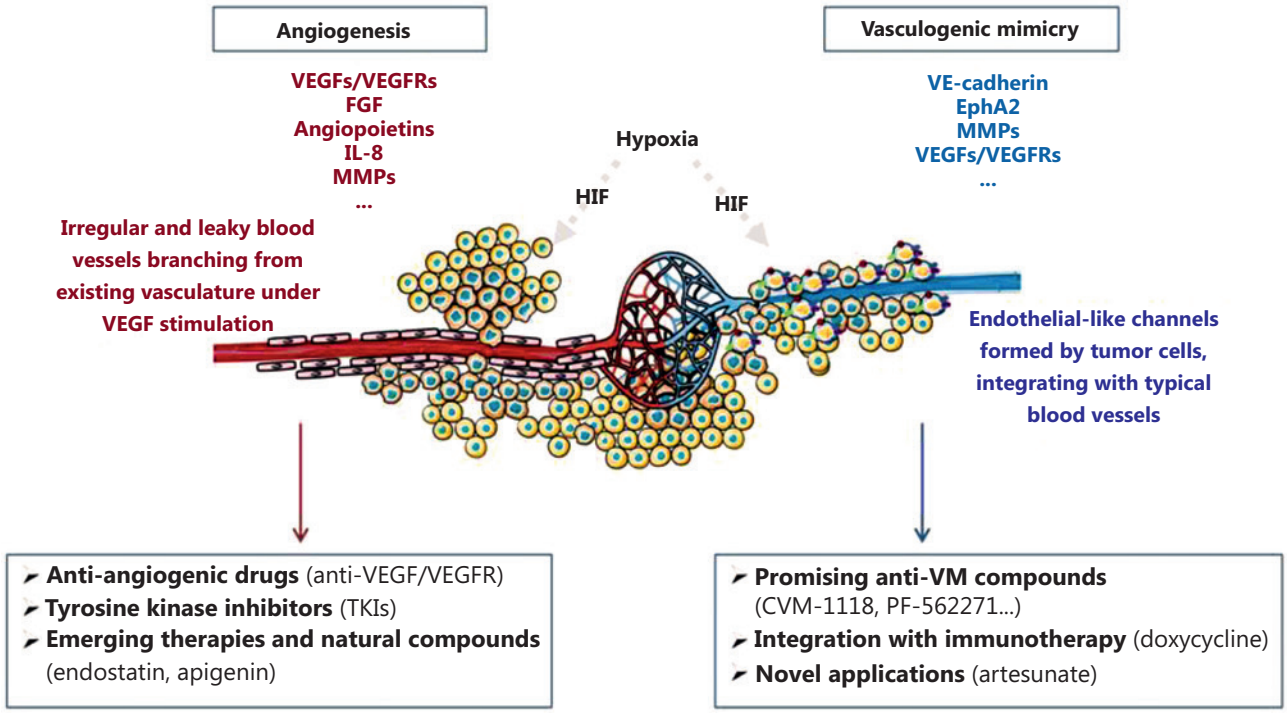

Figure 4 Melanoma: Vascular strategies in tumor progression and therapeutic resistance. The figure illustrates the dual vascularization mechanisms in melanoma (classical angiogenesis and VM). Tissue hypoxia stimulates both angiogenesis and VM. Traditional angiogenesis is primarily driven by VEGF/VEGFR signaling, leading to endothelial cell proliferation and formation of new blood vessels. In contrast, VM is an alternative, non-endothelial-dependent process in which highly plastic melanoma cancer stem cells (MCSCs) form perfusable vascular-like networks, mimicking endothelial functions. This process is supported by specific molecules, including VE-cadherin and EphA2. The figure schematically depicts the current therapeutic strategies targeting angiogenesis and potential therapeutic options to counteract VM. The figure was partly generated using Servier Medical Art, provided by Servier and licensed under a Creative Commons Attribution 3.0 unported license (https://smart.servier.com/). EphA2, Eph receptor A2; HIF, hypoxia-inducible factor; IL-8, interleukin-8; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors.

Conclusions

Angiogenesis and VM are pivotal mechanisms in melanoma progression, having distinct yet interconnected roles in tumor vascularization, metastasis, and therapeutic resistance. Melanoma angiogenesis relies on a delicate equilibrium of pro- and anti-angiogenic factors, disrupted by elevated VEGF-A expression and hypoxia-inducible signaling. VEGF family members and VEGF receptors facilitate endothelial proliferation, migration, and survival, while also enhancing immune evasion and promoting metastasis through lymphangiogenesis. In addition, alternative angiogenic mediators, including angiopoietins, FGFs, and MMPs, provide complementary pathways sustaining vascular remodeling. This dynamic network underscores the redundancy in the melanoma' pro-angiogenic machinery, complicating therapeutic targeting. VM represents an alternative perfusion strategy mediated by plastic tumor cells acquiring endothelial-like phenotypes. Key mediators of VM include VE-cadherin, EphA2, and MMP-14, which collectively facilitate the formation of perfusable tubular structures. Hypoxia acts as a critical driver of VM, stabilizing HIFs and modulating downstream pathways, such as PI3K/AKT and RAS/ERK. The TME further exacerbates VM by inducing EMT and enhancing CSC plasticity. Despite significant progress, therapeutic strategies targeting angiogenesis, such as VEGF-A inhibitors, have shown limited efficacy in melanoma due to compensatory mechanisms, like VM. This adaptive resistance highlights the need for dual-targeting approaches that address angiogenesis and VM pathways. In addition, the role of CSCs and the perivascular niche in maintaining VM emphasizes the potential of targeting stem-like tumor populations to mitigate therapeutic resistance.

Several studies are currently investigating the relationships between the immune microenvironment, angiogenesis, and VM associated with melanoma, as evidenced by clinical trials combining immunotherapeutic and anti-angiogenic agents (**Figure 4**). Furthermore, the recent literature includes numerous *in vitro* and animal model studies aimed at validating novel combined therapeutic strategies[122,123,243]. As previously reported, VEGFR-1 has a key role in both angiogenesis and VM, the activation of which is involved in recruiting myeloid progenitors that infiltrate the tumor. The mAb, anti-VEGFR-1 D16F7, has been shown to enhance the antitumor activity of anti-CTLA-4 and anti-PD-1 mAbs in preclinical models[243].

In addition, a study involving MDSCs demonstrated involvement not only in angiogenesis but also VM. Preclinical studies have shown that doxycycline (DOX) selectively suppresses MDSCs without affecting T cells. Moreover, pretreatment with DOX substantially reduces the ability of MDSCs to promote VM while also enhancing the antitumor activity of PD-1 inhibitors[122].

A crucial aspect to consider is the potential side effects associated with drug combinations. In a recent study, Bu and colleagues addressed adverse events related to anti-VEGF and anti-PD-1/PD-L1 combination therapies. Bu et al. proposed that reducing the expression of innate anti-PD-1 resistance signatures by inhibiting key pathways associated with VEGFA and TGF-β could represent a promising strategy to improve clinical outcomes in melanoma patients treated with ICIs[244].

Systemic inhibition of VEGFA, either alone or in combination with ICIs, is generally well-tolerated by patients. The most frequently reported adverse effects include hypertension and proteinuria, which have also been observed with anti-VEGFA monotherapy and are generally manageable[244]. Overall survival benefits with a single VEGFA-targeting agent have historically been limited in melanoma[245]. However, several ongoing clinical trials are currently evaluating the efficacy of combining anti-VEGFA and anti-PD-1/PD-L1 therapies in MM (NCT02681549, NCT04356729, NCT03175432).

Future research must focus on elucidating the crosstalk between angiogenesis and VM, particularly the shared regulators and signaling pathways. Comprehensive molecular profiling may uncover novel biomarkers predictive of VM and metastatic potential, enhancing the efficacy of diagnostic and therapeutic interventions. As melanoma continues to exploit vascular adaptations, innovative therapies targeting these mechanisms could significantly improve patient outcomes.

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Conflict of interest statement

The authors affiliated to the IRCCS Istituto Tumori 'Giovanni Paolo II', Bari, are responsible for the views expressed in this article, which do not necessarily represent the Institute.

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