Endothelial cell dysfunction in cancer: a not-so-innocent bystander

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ABSTRACT

The body's homeostasis depends on the vascular endothelium, which controls angiogenesis, vascular tone, inflammation, cell trafficking, hemostasis, and the movement of nutrients and waste out of the body. Endothelial cells (ECs) are the primary gatekeepers of many of these vessel wall functions, despite only having a single cell's thickness. Normally quiescent ECs in the context of cancer are activated by anti-cancer therapies, the tumor microenvironment, and factors secreted by the tumor. Crucially, this dysfunctional endothelium actively participates in tumor metastasis and progression rather than just acting as a passive bystander. Compared to the healthy vasculature, ECs in the tumor vasculature are heterogeneous and have a different gene expression profile. Tumor-associated ECs, in particular, exhibit increased pro-angiogenic characteristics and upregulated expression of adhesion molecules and proinflammatory cytokines, facilitating the intra- and extravasation of spreading tumor cells. Furthermore, the downregulation of important anticoagulant molecules and increased endothelial secretion of prothrombotic molecules can directly encourage cancer-associated thrombosis. Many anti-cancer therapies are also less effective in their delivery and function when there is dysfunction in the tumor endothelium. The review highlights some of the most recent research showing how tumor-associated ECs influence angiogenesis, inflammation, coagulation, and metastasis to contribute to the progression of tumors. Undoubtedly, a better understanding of how the tumor microenvironment subverts quiescent ECs and how phenotypic alterations in the vessel wall support the survival and spread of tumor cells will aid in the identification of new therapeutic targets to slow the advancement of cancer.

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Introduction

The vascular endothelium is the largest organ in the body. The total surface area of the vessel wall has been estimated to be 20 times the size of a tennis court and is lined with over one trillion endothelial cells (ECs).[1] These highly specialized cells are key in maintaining vessel homeostasis, regulating vessel integrity and barrier function, contributing to immune-cell trafficking, and facilitating nutrient delivery, and waste removal.[2] ECs display a high degree of plasticity and are responsive to environmental stimuli including infection, drugs, and oxygenation status all of which can feature in patients' cancer journey.[3] Consequently, the endothelium can become significantly dysregulated by tumor-specific factors as well as anti-cancer therapies, and in turn promote tumor proliferation, angiogenesis, chemoresistance, and metastasis.[2,4]

Additionally, endothelium plays an important role in maintaining the balance between hemostasis and thrombosis.[5] Malignancy is a key driver of both arterial and venous thrombosis which not only contributes to the overall disease burden and impacts anti-cancer treatments but is the second leading cause of death for these patients.[6] While the etiology of cancer-associated thrombosis is certainly multifactorial, EC activation and damage play a significant role. Despite all this, little consideration is given to the vasculature or tumor-associated ECs (TECs) in current treatment strategies. Crucially, cancer may not only alter the function of the endothelium within the primary tumor but also systemically throughout the body, thus priming the formation of the pre-metastatic niche, facilitating extravasation, and survival of disseminated tumor cells.[7]

Rather than being a binary event, EC activation is more of a graded response. For example, activation can be specific to the stimulus and may occur locally, as seen in atherosclerosis, or systemically as seen in sepsis.[8] In the setting of cancer

specifically, EC activation has been reported to result in loss of tight- and adherens junctions, permitting EC migration and formation of new blood vessels. The mediators of endothelial activation include a diverse array of factors such as changes in shear stress induced by compression forces of a large solid tumor or a variety of proinflammatory molecules such as interleukins and cytokines, including transforming growth factor beta (TGFβ), all of which can be secreted by the tumor cells directly or secreted by tumor-associated macrophages within the tumor microenvironment (TME). Other means of EC activation that have been reported include elevated tumor secretion of angiogenic mediator, vascular endothelial growth factor (VEGF), or tumor-induced hypercoagulability resulting in thrombin-mediated protease-activated receptor (PAR) signaling on the endothelium. Finally, the direct cytotoxic effects of chemotherapy agents also have a significant impact on endothelial function.[9] This prolonged chronic EC activation also significantly impacts blood vessel morphology and contributes to poor drug delivery to the tumor. Deformed branches with poor coverage of pericytes and remodeled basement membranes result in leaky endothelial vessels, with increased interstitial pressure, decreased blood flow, and perfusion into the tissue.[10,11] This culminates in a hypoxic TME which further propagates EC dysfunction and contributes to poor drug delivery and efficacy.[11]

In this review, we discuss how malignancy can significantly disrupt endothelial homeostasis to promote angiogenesis, thrombosis, inflammation, and metastasis, which ultimately contribute to cancer progression. This also shines some light on novel therapeutic avenues aimed at vasculature normalization in cancer that are under investigation.

Angiogenesis

Tumors that excess 1-2mm^3 switch to an angiogenic phenotype to meet growing metabolic demands.[12] To this end, EC angiogenesis within the TME is orchestrated by a variety of mediators including VEGF, interleukin-8 (IL-8), angiopoietins (Ang), platelet-derived growth factors (PDGF) and TGFβ-1.[13] Elevated plasma levels of these factors are associated with a poorer prognosis and more aggressive tumor phenotype.[14,15] Consequently, anti-angiogenic therapies, including anti-VEGF antibody bevacizumab, were an attractive and promising addition to the oncologist's armamentarium. Despite the

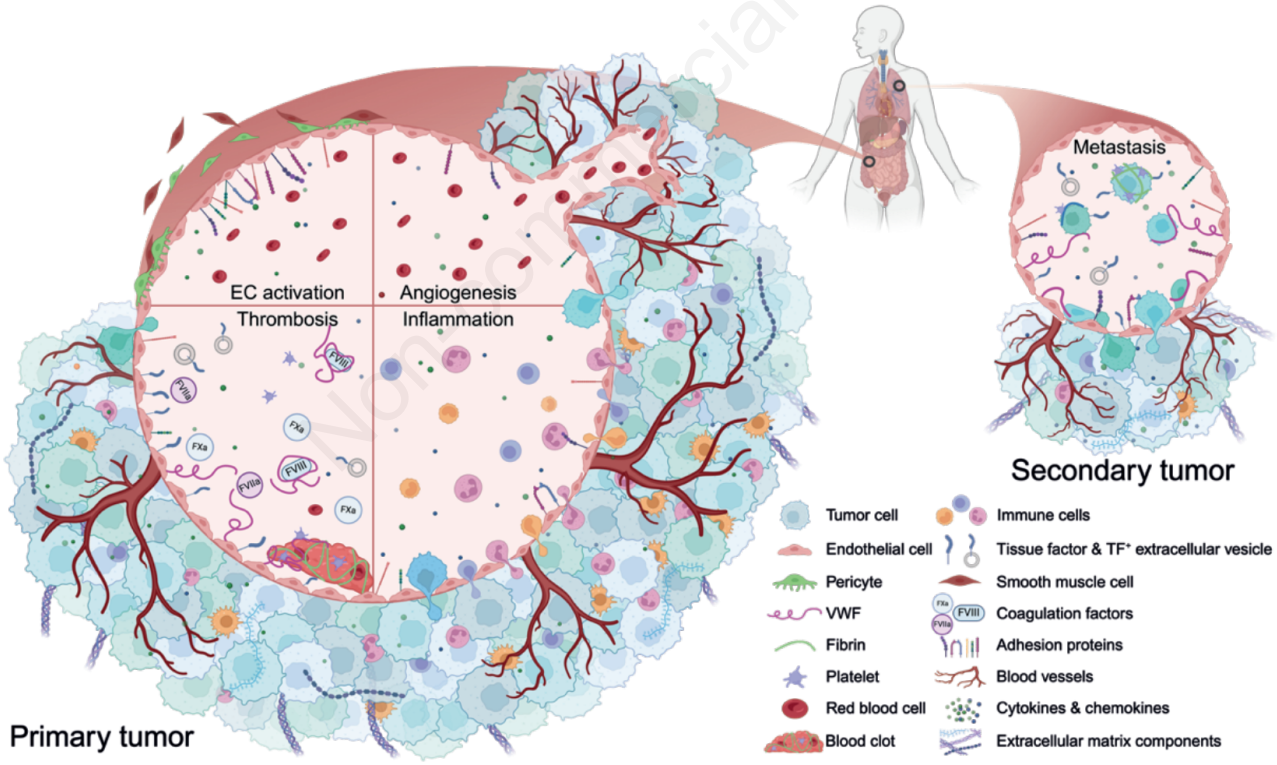

Figure 1. Schematic overview of endothelial cell dysfunction in the contribution to tumor progression. In the primary tumor, endothelial cell (EC) activation results in increased expression of adhesion molecules, secretion of several cytokines and chemokines as well as enhanced vascular permeability mediated by loss of interactions between ECs, smooth muscle cells and pericytes. Tumor-associated ECs display enhanced proliferation and migration properties, contributing to neovascularization within the tumor to support tumor growth. A pro-inflammatory phenotype is also a hallmark of ECs within the tumor vasculature, with increased recruitment and activation of immune cells to the tumor microenvironment. Tumor-associated ECs promote a prothrombotic milieu, with elevated tissue factor expression on the endothelium and enhanced von Willebrand factor/factor VIII secretion. Furthermore, the endothelium prepares the premetastatic niche and facilitates homing and transendothelial invasion of circulating tumor cells.

mechanistic rationale for these anti-angiogenic agents, they had limited clinical efficacy.[16] The precise biological mechanisms underpinning tumor neovascularization remain unclear, however recently, TECs have been postulated to contribute to resistance to anti-angiogenic therapies. For instance, targeting ECs with an anti-VEGF antibody in mice with glioblastoma did not significantly reduce tumor vascularization owing to the fact that expression of its specific receptor (VEGFR) was decreased via PDGF-mediated differentiation of ECs towards a mesenchymal phenotype.[17] TECs consist of a distinct and heterogeneous population of cells that are unique to the TME, recognized by the irregular thickness of the vessel, loose pericyte binding, hyperpermeability and a stiffened extracellular matrix.[18] Consequently, blood flow within tumor vasculature is disorganized creating a hypoxic TME, which affects the efficient delivery of chemotherapies, and the infiltration of immune cells. In fact, up to 40% of invasive breast cancer tumors exhibit hypoxic regions resulting in the upregulation of hypoxia-inducible transcription factor (HIF), thus further stimulating angiogenesis. This reciprocal cycle has been shown to contribute to drug resistance in breast tumors.[19]

Compared to normal ECs, TECs display elevated expression of cancer stem-like markers endoglin, endothelial protein-disulfide isomerase, and aldehyde dehydrogenase (ALDH), associated with high proliferative capacity.[20,21] For instance, $ALDH^{high}$ TECs were able to form tubular networks on Matrigel and were more resistant towards the 5-Fluorouracil.[20,22] Furthermore, some TECs display enhanced angiogenic potential with elevated expression of VEGFR, TIE2, Ang1, E-selectin and intercellular adhesion molecule-1.[23] In addition, TECs help recruit hematopoietic cells and endothelial progenitor cells to the TME to maintain tumor angiogenesis.[24] Interestingly, TECs isolated from highly metastatic tumors displayed increased pro-angiogenic properties and increased chemoresistance than TECs isolated from low metastatic tumor *in vivo*, highlighting their role in supporting the TME.[25] As a result, TECs mirror a chronically activated endothelium with high angiogenic potential (Figure 1).

To improve the understanding of TEC heterogeneity, recent studies have focused on single-cell transcriptomics.[26,27] Single-cell RNA sequencing of malignant and non-malignant ECs from lung and breast cancer patients as well as tumor-bearing mice has helped identify subpopulations of ECs with different phenotypes and proportions. These data may provide a basis for new therapies to specifically target TECs. For instance, TECs display a high glycolytic metabolic profile. The inhibition of the upstream glycolytic activator PFKFB3 upregulated VE-cadherin expression on ECs. Consequently, a more mature vascular endothelium was present with a restored barrier function, resulting in fewer metastases and improved chemotherapy delivery.[18] Checkpoint inhibitors are an ever-growing family of anti-cancer drugs. However, tumors can become resistant when infiltration of immune cells is blocked. Interestingly, the high expression of Ang2 in the TME can cause T-cell exclusion in melanoma tumors. Improved T-cell infiltration was observed when the Ang/TIE2 signaling axis on ECs was inhibited, consequently increasing the sensitivity of melanoma cells towards the checkpoint inhibitor anti-PD1.[28] Collectively, this highlights the therapeutic potential in targeting TECs in combination with standard cancer treatments to improve efficacy.

More recently, studies show plasticity of tumor cells and how they can circumvent anti-angiogenic therapy by acquiring a pseudo-endothelial-like phenotype, coining the term 'vasculogenic mimicry'.[29,30] These endothelial-like tumor cells form a stable tubular structure, resulting in 'mature' vessels with sustained blood flow.[29] To date, knowledge on the underlying mechanisms of vasculogenic mimicry is limited, however, in melanoma, there are indications that they might have derived from cancer stem cells, as they are CD271 positive; or via Oct4a in lung cancer stem cells, respectively.[30,31] Furthermore, hypoxia-mediated HIF-1α can transdifferentiate cancer stem cells into an endothelial-like phenotype.[32] Clinically, vasculogenic mimicry is associated with a poorer prognosis in cancer patients, *e.g.*, lung adenocarcinoma.[33] These studies highlight that an improved understanding of the tumor vasculature and its heterogenic population of ECs will be key to help identify novel therapeutic targets and attenuate the pro-angiogenic TME.

Thrombosis

Plasma of cancer patients displays a hypercoagulable state, and approximately 20% of cancer patients develop thrombosis.[6] Specific anti-cancer treatment regimens also exacerbate this risk, for example, chemotherapies can activate the endothelium, inducing a pro-inflammatory and pro-thrombotic state.[6] The etiology of cancer-associated thrombosis remains poorly understood but is certainly likely to be multifactorial. Intriguingly, however, this interplay between cancer and coagulation appears to be bidirectional, with coagulation activation providing positive feedback for cancer progression.[34] Within the circulation, coagulation factors including fibrin(ogen), as well as platelets can protect tumor cells from attack by immune cells, thereby facilitating successful metastasis (Figure 1).[35] Furthermore, coagulation factor Xa (FXa) expressed on tumor-associated macrophages contributes to tumor-evasive immune signaling, thus limiting the efficacy of immune checkpoint inhibitors.[36]

In cancer, chronically activated ECs display elevated secretion of von Willebrand factor (VWF) and factor VIII (FVIII).[37,38] Both VWF and FVIII have been associated with significant risk factors for cancer-associated thrombosis.[39] Furthermore, high VWF plasma levels are associated with poor overall survival in cancer patients. VWF-multimers secreted from ECs can tether circulating platelets and promote aggregation.[5] Bauer *et al*. demonstrated that VWF-mediated platelet aggregation occurs via melanoma-derived VEGF-A, which promotes the release of VWF from ECs in mice. The inhibition of VWF secretion by treatment with low molecular weight heparin (LMWH), which sequesters melanoma VEGF-A, significantly attenuated tumor metastasis as well as angiogenesis *in vivo*.[40] In addition, we have shown that these adhesive VWF multimers also contributed directly to circulating breast tumor cell binding under shear flow, a key prerequisite step for metastasis.[13] In support of this, several studies have reported reduced metastasis *in vivo* following treatment with anti-VWF antibodies.[38,41]

A well-studied driver of hypercoagulability in malignancy is tissue factor (TF), the initiator of the extrinsic coagulation

pathway.[34] In cancer, elevated TF expression strongly associates with cancer proliferation and progression.[42] In tumors, hypoxia-mediated signaling increases TF expression in tumors and stromal cells, like monocytes and ECs. This leads to the production of proangiogenic factors like VEGF, CXCL1, and IL-8, consequently leading to neovascularization.[34] Furthermore, cancer cells can secrete TF-positive extracellular vesicles (TF^+ EVs). *In vitro*, these TF^+ EVs were endocytosed by ECs and recycled to the cell surface, resulting in procoagulant phenotype while also increasing E-selectin expression and IL-8 secretion culminating in enhanced angiogenesis, endothelial permeability, and metastasis.[43]

TF-mediated coagulation can be inhibited by EC-expressed tissue factor pathway inhibitor-1 (TFPI-1) as it directly suppresses FXa activity and the TF/FVIIa complex.[44] Downregulation of TFPI1 increases the invasive and migratory capacity of tumor cells via integrin-mediated adhesion.[44] In breast cancer patients reduced expression of TFPI1 in tumors is associated with poor prognosis.[45] Furthermore, soluble TFPI in the plasma of non-small cell lung carcinoma patients revealed to be a biomarker for both thrombosis and metastasis.[46] Treatment with a chemically modified LMWH, termed S-NACH, increased TFPI1 expression on ECs and consequently reduced hypercoagulation and metastasis of pancreatic tumor cells *in vivo*.[47,48] Although TFPI1 is predominantly expressed on ECs, and exerts its anticoagulant effects there, it is unclear if these associations come from tumor- or EC-expressed TFPI1.

Anticoagulants, as part of anti-cancer therapies, increased the potential bleeding risks, and their use thus far has been limited to thromboprophylaxis in high-risk cancer-associated thrombosis patients.[36] Notwithstanding this, preclinical studies have provided evidence of anti-tumor properties for LMWH, with improved vessel barrier function, inhibition of angiogenesis and transendothelial migration.[13] Furthermore, LMWHs have been shown to inhibit the expression of selectins on ECs, and block the interaction between Integrin $\alpha_4\beta_1$ and vascular cell adhesion protein 1 (VCAM-1) on tumor and ECs, respectively. Correspondingly, reduced tumor-endothelium adhesion-mediated migration has been observed following LMWH treatment.[49] Treatment of breast cancer with LMWH in combination with chemotherapeutic agents paclitaxel or doxorubicin reduced tumor growth and liver metastasis in a mouse xenograft model, as LMWH improved intratumoral drug delivery.[50] Similarly, the combination of LMWH with checkpoint inhibitor anti-PD1 reduced tumor growth and metastasis of murine colon adenocarcinoma. These tumors displayed enhanced lymphocyte infiltration, with improved tumor vascular normalization by LMWH.[51] These data suggest a novel therapeutic strategy wherein combining anticancer therapies with LMWH might possess great potential to improve drug efficacy and attenuate disease progression and metastasis.

Inflammation

Under normal conditions, the endothelium appears to serve a more tumor-suppressive role. For example, the secretome from quiescent tumor-native ECs reduced breast and lung tumor cell proliferation and invasion *in vitro* and *in vivo* by reducing NF-κB and STAT3 inflammatory signaling.[52] Interestingly, however, silencing of endothelial perlecan, a heparan sulfate proteoglycan, reversed these anti-inflammatory effects, increasing tumor cell growth and invasiveness in a manner that was dependent on the pro-inflammatory cytokine IL-6, thus promoting metastasis in lung carcinoma xenograft models. The biology of EC dysregulation in the tumor vasculature is not fully understood, but pro-inflammatory mediators secreted by the tumor cell and other stromal cells within the TME are postulated to play a role (Figure 1). For example, tumor cell-derived CCL2 directly activates CCR2 on ECs, thereby enabling efficient tumor cell extravasation.[53] In fact, colon carcinoma extravasation and metastasis were highly dependent on endothelial expression of CCR2 which induced downstream JAK2, STAT5, and MAPK signaling pathways to increase vessel permeability and transendothelial migration.

In addition, direct tumor-endothelial interactions can also augment vascular homeostasis. For example, cell-cell interactions mediate increased Notch1 activation in the tumor microvasculature of lung, breast, colorectal, ovarian cancer and malignant melanoma.[54] This significantly impacts vessel permeability and induces the expression of several endothelial cytokines and chemokines, including IL-1β, CCL1, CXCR4 as well as upregulating adhesion molecule VCAM-1. Collectively, this pro-inflammatory endothelial phenotype has been shown to promote neutrophil infiltration, tumor-endothelial adhesion and migration, lung colonization, and metastasis in murine models of lung carcinoma and melanoma.[54]

Recent in-depth single-cell transcriptomic analysis of TECs has revealed enhanced gene signatures for leukocyte recruitment, cytokine production and scavenger activity.[27] There is evidence to suggest that the upregulation of these inflammatory processes can directly promote cancer aggressiveness.[55] In particular, genes related to TNF-α receptor signaling pathways including NF-κB and interferon family members were all enriched in TECs isolated from tumor-bearing mice.[56] Crucially, TEC secretome accelerated the growth of human colon tumors in immunosuppressed mice. Moreover, Pitroda *et al*. reported a panel of six inflammatory endothelial-derived genes which displayed a significant prognostic value in predicting overall survival in breast, lung, and glioma cancer patient cohorts. Collectively, these findings suggest that the pro-inflammatory tumor milieu, propagated at least in part by dysfunctional tumor endothelium, contributes to cancer progression and poorer patient outcomes.

ECs can also negatively influence immune cell recruitment and activation within the TME. For instance, TECs can display immunosuppressive properties with repressed leukocyte infiltration. Altered T-cell responses have been described due to elevated expression of inhibitory immune checkpoints from ECs, like programmed death-ligand-1/-2, IL-10 or prostaglandin-E2.[57] Moreover, Notch1 signaling in ovarian cancer cells can induce endothelial expression of CXCL2. This triggers the infiltration of monocyte-derived macrophages into the TME and promotes an immunosuppressive environment.[58] Similarly, in a murine model of glioblastoma, EC-specific knockdown of IL-6 inhibits macrophage polarization to an immunosuppressive phenotype, thus improving survival *in vivo*.[59] Additionally, EC hyperglycolysis inhibition with Osimertinib in colorectal tumor-bearing mice restored

vasculature and immune infiltration. Combinational therapy of Osimertinib with PD-1 blockade even showed synergistic effects with significantly smaller tumor volumes *in vivo*.[60] The ability of ECs to contribute to an immunosuppressive environment and altered T-cell responses is likely to impact the efficacy of immunotherapies,[61] and a combinational approach of targeting both the vasculature and tumor cells could be beneficial.

Dysregulated ECs can facilitate resistance to chemotherapy through altered pro-inflammatory signaling. For instance, studies have shown that chemotherapeutic drug exposure triggers TECs to secrete TNF-α and promotes CXCL1/2 expression in both breast and lung tumor cells, contributing to chemoresistance and relapsed disease.[62] Similarly, targeting focal adhesion kinase (FAK) in TECs promoted tumor cell sensitization to doxorubicin and radiation-based therapies, thus inhibiting tumor growth in murine models of melanoma and lung carcinoma.[63] The inhibition of endothelial FAK was shown to reduce NF-κB signaling, therefore resulting in a significant decrease in pro-inflammatory cytokines, including IL-1α, and IL-6, again highlighting the interplay between tumor biology and its inflammatory microenvironment. The improved understanding of the mechanisms through which the tumor vascular niche drives resistance may help identify novel drug targets to mitigate refractory and relapsed disease for cancer patients.

Metastasis

Classically, metastatic dissemination is focused on the tumor cell, how it remodels the extracellular matrix, invades and transmigrates through the endothelial layer into the bloodstream. At a distant organ, the circulating tumor cell will cross the endothelial barrier once more to establish micro-metastatic foci.[64] Even in this simplistic view, it is clear that tumor-endothelial interactions play a key role in metastatic spread. The immature structure and organization of tumor-associated vasculature is postulated to enable enhanced migration of tumor cells through its leaky barrier (Figure 1). Moreover, the secretome of TECs can directly modulate the invasiveness of tumor cells.[65] For example, Akt signaling in TECs isolated from highly metastatic tumors was significantly upregulated compared to TECs from low metastatic tumors. Consequently, the secretion of cytokines such as IL-6, and matrix metalloproteases (MMPs), including MMP-9, are known to drive invasion in tumors.[24,25] Epigenetically upregulated expression of biglycan from TECs activated NF-κB and ERK signaling pathway in tumor cells increasing the number of circulating tumor cells and lung metastases *in vivo*. Accordingly, biglycan plasma levels in patients correlated with the presence of metastatic disease.[66] Furthermore, vascular expression of CXCR7 was associated with improved tumor cell survival and metastasis. Stacer *et al*. reported that endothelial-specific knock-out of CXCR7 in mice was associated with significantly greater recurrence of breast cancer following resection, increased numbers of circulating tumor cells, and enhanced spontaneous metastases.[67]

As part of metastasis, tumor cells undergo epithelial-to-mesenchymal transition (EMT),[42] during which they lose cell-cell contacts, and enhance migratory and invasive properties. TECs can directly potentiate EMT via secretion of epidermal growth factor, plasminogen activator inhibitor-1, and CCL5.[65] In addition, TECs are capable of remodeling the extracellular matrix through the secretion of ADAM17 and MMPs,[25] which leads to the release of key growth factors including TGFβ, fibroblast growth factor-2, and insulin-like growth factor-1, consequently creating a positive feedback loop to further augment tumor cell migration.[68] *Vice versa*, tumors can induce endothelial-to-mesenchymal transition (EndMT) via TGFβ1/2, Wnt/β-catenin, and Notch signaling. This disrupts tight junctions, causing leaky vessels and increased tumor transendothelial migration.[65] Additionally, knockout of EC-specific c-MET in glioblastoma, restored temozolomide sensitivity *in vivo*, which resulted in smaller tumors and improved vasculature.[69] Likewise, the restoration of the brain microvasculature via inhibition of endothelial rho kinase ROCK suppressed migration of small cell lung cancer cells.[70] EndMT can drive ECs to transition to cancer-associated fibroblasts (CAFs). These cells correlate with increased tumor development and growth.[71] Approximately 40% of all CAFs are derived from ECs.[68,71] The elevated secretion of MMPs allows CAFs to remodulate the extracellular matrix.[71] Erdoğan *et al*. have shown that patient-derived CAFs produce a stiff, fibronectin-rich matrix in the tumor milieu, where fibronectin orientation laid down by the CAFs promotes directional migration for invasive prostate tumor cells.[72]

ECs can also actively contribute to the formation of the pre-metastatic niche with the primary tumor-secreting factors that precondition distal tissues for the arrival of disseminating tumor cells.[73] Specifically, tumors secrete extracellular vesicles and inflammatory cytokines to enhance vascular permeability and thus promote tumor cell extravasation. For example, TGFβ-mediated upregulation of angiopoietin-like 4 in breast tumor cells decreased cell-cell junctions in ECs *in vitro*. This directly facilitated tumor colonization in the lungs of murine breast cancer models.[74] Similarly, endomucin, which is involved in the tube formation of ECs, is downregulated in several cancers. Deficiency of endomucin on ECs results in increased vascular permeability and recruited tumor-supporting N2-type neutrophils at the premetastatic niche in a murine lung carcinoma model.[75] Direct interaction between disseminating tumor cells and normal, tumor-naïve ECs at the premetastatic niche can also promote drug resistance. Specifically, breast tumor integrin $\alpha_v\beta_3$ facilitates interaction with endothelial-expressed VWF within the perivascular niche of the bone marrow.[76] Targeting this axis via knockdown of VWF expression or $\alpha_v\beta_3$ blocking antibody sensitized breast tumor cells to doxorubicin and reduced bone marrow metastasis *in vivo*. Further studies are warranted to better understand tumor-specific factors that induce vascular dysregulation at distal tumor-free sites, as these may be key to attenuating metastasis at early disease stages.

Overall, considering the tumor endothelium in the design and development of novel anti-cancer strategies may not only improve the targeting and delivery of standard-of-care treatments but also serve to attenuate pro-tumor properties of the vasculature. However, as previously described, TECs are a heterogeneous population with altered genetic, transcriptomic, and metabolomic profiles.[57,77] On top of that,

it is entirely likely that TECs are tumor-subtype specific.[26] Recent reviews have extensively described TEC heterogeneity and how these cells could be reprogrammed to restore EC function.[18,57,77] Further studies defining TECs in specific cancers will help elucidate their complex contribution to disease and potentially identify specific means by which to target them and contribute to novel therapeutic approaches.

Conclusions

The endothelium plays an important role in modulating tumor progression. There is a bidirectional crosstalk between the vasculature and tumor cells with dysfunctional ECs promoting angiogenesis to sustain tumor growth, fostering a pro-inflammatory TME and a systemic pro-thrombotic state to aid dissemination and drug resistance. Moreover, enhanced expression of adhesion molecules facilitates direct tumor-endothelial binding and contributes to transendothelial migration and metastasis. The dysregulated endothelium can no longer be considered an epiphenomenon of malignancy but rather an active player in tumor progression. Further studies will be required to help identify novel therapeutic targets aimed at vasculature normalization in cancer. Importantly this approach may also help improve the delivery and efficacy of current standard of care treatments for patients with cancer.

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