

The Stem Cell Vascular Niche in Brain Tumorigenesis

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Abstract

The cancer stem cell vascular niche is a physical and biological unit composed of a conglomerate of innate cancer stem cells and progenitor cells that are recruited into this dynamic and highly complex milieu. Collectively they modify the extracellular matrix and form a permissible microenvironment to facilitate the renewal, proliferation, invasion, and differentiation of the cancer stem cells, and those of the auxiliary cells. The angioarchitecture within the tumor is grossly abnormal as these vessels are of varying caliber and arborization. These abnormal tumor vessels can be generated from endothelial progenitor, hematopoietic, monocytic and mesenchymal stem cells derived from the bone marrow (BM). Recent studies have observed that tumor endothelium is also derived from cancer stem cells transforming our understanding of the intimate relationship between cancer stem cells and vascular niche. Given these observations, it is conceivable that mutation at the level of vasculature may translate to an abnormal vascular niche discharging unregulated stem cell signals and thus propel aberrant cancer stem cells to achieve their lethal malignant potential. In this review we summarize the cellular and molecular components of stem cell vascular niche with a special emphasis on brain tumors.

Categories: Neurosurgery, Oncology

Keywords: vascular niche, glioma, neural stem cell, cancer stem cell, angiogenesis, endothelium

Introduction And Background

The idea of cancer initiating cells associated within the tumor-angioarchitecture was first mentioned in the monograph, *A classification of tumors* by Bailey and Cushing in 1926 [1]. They described the unipolar astroblasts whose "tails become attached to the walls of capillaries". The temporal-causal relationship of vascular development and tumorigenesis was indisputably demonstrated by Folkman, and refined by Jain and others [2-3]. In late 1990s, Holash, et al. suggested that dormant tumor cells commonly resided in the proximity of blood vessels, and as the tumor expands they "co-opt" new vessels toward themselves [4]. The glioblastoma (GBM) vessels are tortuous, highly permeable and characterized by abnormalities in their cellular components and basement membrane. These vessels are used as a means to support their needs and as conduit along which they invade and proliferate. These work underpinned the functional relevance of tumor vascular niche. Recently Gilberston and others [5] have shown that brain cancer initiating cells – the cancer stem cells (CSC) are closely located with pre-existing vascular trees. Together they re-shape the neo-angioarchitecture and by encompassing auxiliary cells and their surround basal-matrix, they form the vascular niche complex where cancer stem cells evolve and propagate. It is the cellular activity within these complexes that dictate the robustness of tumorigenesis. It is plausible that within these niches cancer stem

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cells remain in a steady state between proliferation and quiescence prior to further expansion and invasion, hence the dormant phase of tumorigenesis.

Review

The cancer stem cell hypothesis

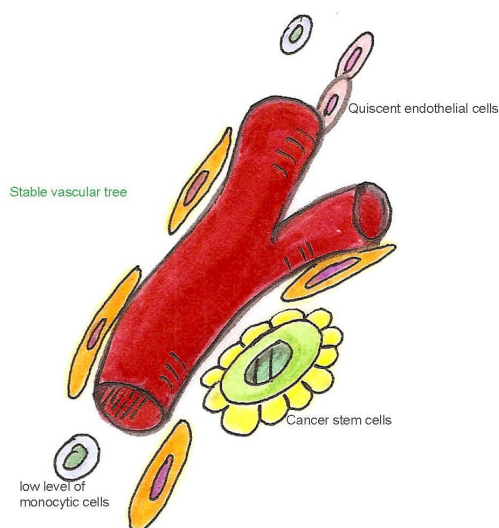
There is a striking resemblance between neural stem cell biology and glioma biology. Both can be identified with similar markers, such as nestin and CD133 [6-7]. In the case of the neural stem cell, the balance between proliferation and differentiation is highly regulated. While in glioma, there is marked dys-regulation of the balance between proliferation and differentiation, resulting in uncontrolled self-renewal and associated tumor growth and incomplete differentiation (Table 1). Recent studies have suggested tumors initiate from cells that harbor chromosomal defects that predispose themselves to further genomic mutation. Accumulated genomic defects eventually reach a threshold where they decouple from physiological cell-cycle regulatory checkpoints and undergo unchecked proliferation [8-9]. Within those cluster of mutated cells lies a subpopulation of tumorigenic cells that shares a number of characteristic similar to stem cells, characters such as the ability to self-renewal, proliferate, invade, and differentiate. This population of "stem-like" cells within the tumor may serve as the reservoir for future cancer-initiating cells. Furthermore, the open chromosomal structure observed in these cells exposes them to the risk of accumulating deleterious mutations over the lifetime of the organism. This accumulation of aberrant genetic changes has been suggested to be the principle cause of cancer formation [10]. This hypothesis suggests that expansion of transformed stem-like cells (cancer stem cells) replenishes the tumorigenic cancer cells that perpetuate the growth of the tumor. Singh, et al. have provided experimental evidence in the role of this sub-population of cells in the initiation of GBM, the most devastating of the brain tumors [11]. Subsequent studies have suggested that this cancer stem cell population may undergo aberrant differentiation in addition to genetic instability and epigenetic change, resulting in cellular heterogeneity that is commonly observed within the tumor mass [12-13].

	Neural Stem Cells Vascular Niche	Cancer Stem Cell Vascular Niche
Anatomical location	Restricted to dentate gyrus and Subventricular Zone	Any region occupying tumor
Epoch	Presents normally during development and adult neurogenic niches	Present only in pathological state of glioma.
Cellular contribution	Minor contribution of vascular endothelium from neural stem cells. Primarily from progenitors of endothelial and its associated axuillary cells	Possible contribution of vascular endothelium from cancer stem cells, in addition to progenitors of endothelial and its associated axuillary cells
Genetical stability	Genetic abnormality is absent	Significant genetic and epigenetic mutation
Vessel architecture	Normal vessels with normal tissue oxygen delivery.	Vessels are highly tortuous and present with tissue hypoxia
Migration	No abnormal migration	Prolific migration and infiltrates normal tissue.

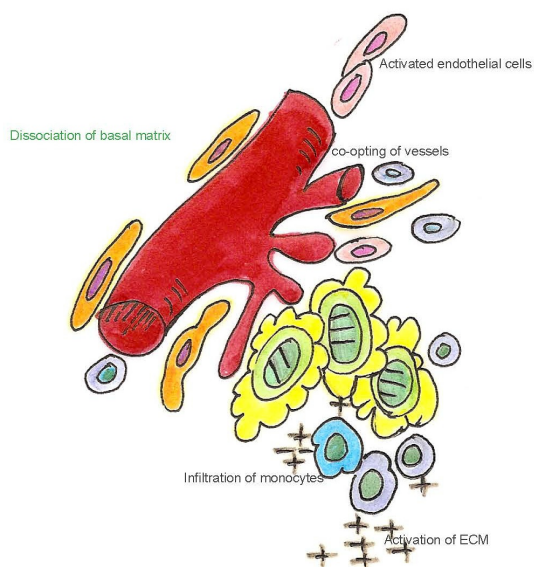
TABLE 1: Difference in vascular niche between normal neural stem cells and cancer stem cells

If cancer is viewed as developmental cues gone awry, then it is not surprising that cancer and stem cells share many molecular mechanisms mediating important cellular processes such as self-renewal, differentiation, and possible "fate determined" migration [14]. Furthermore, tumors exhibit a cellular hierarchy similar to that found during normal development [10]. This hierarchy allows tumors to recruit new blood vessels and coax other cell types to the tumor milieu. This system functions independently of the normal physiologically regulated systems (Figure 1).

Dormant stage



Vascular niche complex



Cancer vascular niche with malignant transformation

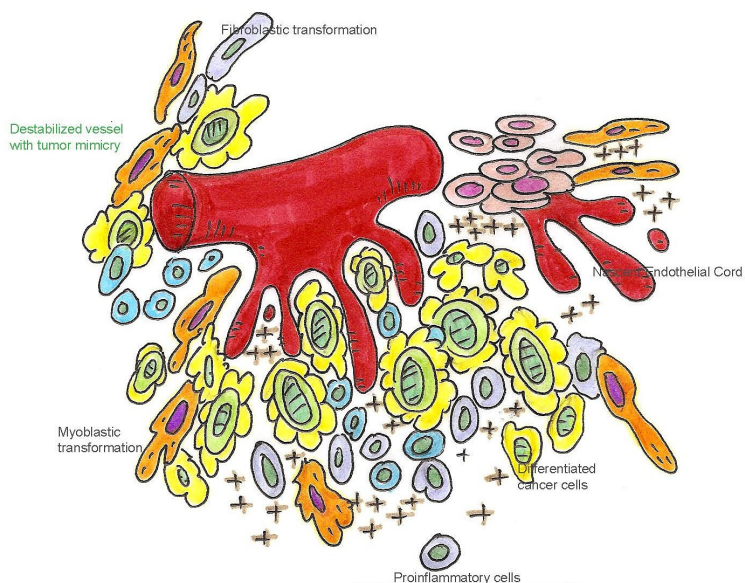


FIGURE 1: Schematic representation of proposed model for

stages of gliomagenesis

Dormant stage Cancer stem cells destined to become glioma are present adjacent to blood vessels. The endothelial cells are quiescent at this stage and the tumor milieu contains low levels of monocytic cells. With increased proliferation of cancer stem cells there is an increased infiltration of monocytes. This is also associated with activation of endothelial cells. With the accompanying breakdown of ECM, the endothelial cells form nascent endothelial cord. The generation of reactive oxygen and nitrogen species aids this process

The cellular constituency of the cancer stem cell-vascular niche complex

Calabrese and colleagues have reported that there is a population of Nestin⁺/CD133⁺ in brain tumor, which is located in areas of increased micro-vessel density [15]. These vessel-associated cancer stem cells were in direct contact with the capillary networks, whereas CD133⁻ cancer cells were diffusely distributed with no apparent vascular localization [16]. Moreover, CD133⁺ tumor cells were shown to home towards endothelial vascular tubes and initiate contact along the entire length of exposed vasculature. The location and microenvironment dependence of these initiating glioma stem cells have also been confirmed in other tumors [17]. In addition to these CD133⁺ cells within the tumor, there exists endothelial progenitors and bone marrow (BM) derived cells. A number of animal models have suggested the contribution of endothelial progenitor and BM-derived cells in tumor neo-vascularization [18-19]. This supports the notion that vasculogenesis is an important epoch in tumor growth.

The role of endothelial progenitor cells in the formation of the vascular niche

It is widely believed that circulating endothelial progenitor cells and bone marrow-derived progenitors home into the site of robust neo-vascularization. This is despite the fact that purified populations of EPC has been challenging to isolate and culture as homogenous populations. Though prominent markers such as CD133 and KDR are expressed by endothelial progenitor cells, these markers are non-specific and label several cells types outside of the classified EPC subtype. Once arriving at the tissue site, under the influence of local VEGF and PDGF, these circulating progenitor cells dock onto the "co-opting" blood vessels, vessels that have partially or completely dissociated basal matrix mediated by E and P selectins [20-21]. The ensuing extravasation forms the initial step in the sprouting of new vessels within the tumor and in their periphery [22]. The evidence for the contribution of BM-derived endothelial progenitor cells (EPCs) in tumor angiogenesis is relatively well-established [23-24]. However, the ontogenesis of these EPCs is still debatable. Most endothelial progenitor cells do not differentiate into mature endothelial cells but may rather affect vasculogenesis by releasing of proangiogenic cytokines. It is plausible that BM derived EPCs are derived from putative hemangioblasts which are the precursors of both hematopoietic and endothelial cell lineages. These hemangioblasts express phenotypic markers of hematopoietic stem cells (HSCs) [25] as well as differentiated endothelial cells [26-27] and are thus antigenically difficult to distinguish from EPCs since both express CD133, a stem cell's marker. Moreover, both cell types may have resided in the same location within the adult bone marrow. Once in peripheral blood, they home to sites of tissue ischemia, trauma, or tumor growth, where they differentiate into endothelial cells to support vascular remodeling [28-30]. Studies in various solid tumors have revealed that EPCs differentiate into mature ECs, and these ECs are incorporated into the lumen of emerging neovasculature [31].

The role of BM-derived cells in the vascular niche formation

BM-derived mesenchymal stem cells (MSCs) also play an important role in post-natal vasculogenesis, notably during tissue ischemia and tumor vascularization. Their primary function is related to the formation of the perivascular cells and the associated matrix. These putative perivascular progenitor cells are recruited by PDGF-stimulated VEGF expression in tumor endothelial cells to support and stabilize the nascent vessels [32]. Although these pericytic cells are loosely associated with tumor blood vessels and reduced in number when compared with normal tissue vasculature [33], they appear to be important cell constituents in tumor angiogenesis [34]. These pericytic cells contribute to the early phase of angiogenic sprouting, tube formation, and survival of the vascular niche within tumors [35]. They are cells that guide the endothelial cell cord at the advancing edge of neovascular formation, and later on they secure the integrity of the nascent vessels. Systemically administered MSCs target sites of growing tumors [36]. Congruent with the hypoxic conditions within gliomas, an associated rise in HIF-1 α expression leads to recruitment of BM-derived MSC to promote neovascularization in GBM via interplay between MMP9 and VEGF [20]. Although MSCs do not express VEGF receptors, Ball, et al. recently identified that VEGF-A can stimulate PDGF receptors, which in turn regulates MSC migration and proliferation [37]. Recent evidences suggest that MSCs may even be the progenitor cells from which fibroblasts within the tumor stroma are derived [38].

Monocytes and fibroblastic cells in the formation of CSC-vascular niche complex

There is a temporal window just prior to the expansion of the tumor mass which enables the incorporation of BM-derived progenitor cells into the tumor vessel-wall [39,40]. Within this window of time, the recruited cells generate a conducive microvascular environment. At that juncture, the pre-existing vessel wall within this defined space serves as an independent niche for the recruitment and insertion of EPCs, MSCs and other monocytic progenitors cells. The recruitment of these progenitor cells by CSCs helps in the establishment of a nascent vascular niche for tumorigenesis. CD11⁺ circulating monocytes recruited into the vascular niche acquire an endothelial-like phenotype and are incorporated both into the lumen and perivascular space. These monocytic cells provide "reconstitute and instructive" signals for tumor establishment [41,42].

An emerging hypothesis states that CSCs drive tumorigenesis by directly inducing an inflammatory phenotype within the cancer stem cell-vascular niche complex, thus catapulting a conducive to an inductive environment [43]. This occurs by recruiting immunocytes and promoting stromal remodeling as seen in aberrant stem cell-vascular niche that contributes to myeloproliferative diseases [44]. The migration of hematopoietic pro-angiogenic cells, most notably macrophages and mast cells, aids in the production of pro-angiogenic factors, proteases, and growth factors responsible for the creation of a microenvironment that stimulates epithelial-cell migration, survival, and proliferation. Of particular importance are monocytic cells such as macrophages, a key component in the cellular constituent of inflammation. In inflammatory tissues, macrophages are predominantly of the M1 phenotype. These cells produce high levels of reactive oxidation species (ROS) and inflammatory cytokines, resulting in potent antimicrobial, immuno-stimulatory and tumor cytotoxic functions. In response to tumor-derived cytokines these macrophages acquire the M2 phenotype [45]. They are a potent source of the mediators that perpetuate the inflammatory process, and they release reactive oxygen and nitrogen species. ROS have also been shown to modify the activity of myeloid-derived suppressor cells (MDSCs). MDSCs are directly involved in tumor angiogenesis; they stimulate angiogenesis and ECM breakdown through the production of angiogenic growth factors and MMPs. Secretion of MMPs and other proteinases by macrophages in the vascular niche enhance cancer-cell motility, dispersion and invasion. The reactive oxygen and nitrogen molecules can directly damage DNA and modify the proteins that are involved in DNA repair. Moreover, MDSCs inhibit anti-tumor immunity. In combination with nitric oxide, MDSC-

derived ROS contribute to the generation of peroxynitrite [46]. The latter causes the nitration of various tyrosines on proteins, including the T-cell receptor CD8. This modification alters antigen recognition and thereby induces T-cell tolerance [47].

In addition to monocytic cells there is influx of fibroblasts, and some of the monocytic cells may undergo epigenetic transformation with fibroblastic/myofibroblastic morphology [48,49]. These cells produce chemokine such as stromal-cell-derived factor1 (SDF1), a mitogen in its own right. Myofibroblast-derived SDF1 promotes the proliferation of mammary carcinoma cells that express its high-affinity receptor CXCR4, and likely contributes to cancer growth through the regulation of angiogenesis by attracting endothelial progenitor cells [50]. Being highly mobile, fibroblasts form the advancing edge of the tumor with the nascent vascular cord in tow. The cancer cells will adhere along these conduits to spread to the surrounding normal tissue ignoring tissue boundary and autonomy that have partly destroyed or interrupted during matrix modification [51].

Cancer stem cells derived endothelium

Recently it has become evident that glioma stem cells have cell lineage potential beyond what was conventionally assigned to them. CD133⁺ glioma stem cells that carry chromosomal abnormalities also generate genetically aberrant endothelial cells that profoundly contribute to the vascular architecture of the glioma [52,53]. Such tumor derived endothelial cells produce VEGF and have the potential to generate highly vascularized anaplastic tumors. When the GBM-derived endothelium was genetically targeted and killed, the entire tumor became necrotic suggesting the vital role the new born endothelium play in the survival of tumor. These studies also highlighted the crucial role of Notch in the transition of tumor stem cells into tumor endothelial cells. It is noteworthy that Notch has been shown to play an important role in modulating cancer stem cell renewal and proliferation. Mutation in Notch leads to uncontrolled proliferation and renewal of cancer stem cells [54].

Molecular regulators of CSC-Vascular Niche Complexes

Hypoxia and its associated signal transduction pathways: Most cells have to be within 100-200 μ m from its blood supply to receive adequate nutrition. Beyond this distance there is a precipitous drop in O₂ diffusion efficiency. Tumors are known to utilize glycolysis to generate lactate from glucose even in the presence of abundant oxygen, a phenomenon known as Warburg effect [55]. This potentially serves two purposes, first it enables the tumor cells to generate intermediates for cells growth and division [56]; second by relying less on mitochondria for ATP generation, and there is high mitochondrial membrane potential conferring apoptosis resistance [57]. These inhibited mitochondria in tumor cells transmit pseudo hypoxic redox signals and activate HIF-1 α even during normoxia [58]. They are coordinately regulated by oncogenes such as PI3K-Akt and Myc [59]. The excess lactate generate by this aerobic glycolysis also promotes angiogenesis and matrix breakdown, events that facilitate metastasis [60]. Glycolysis also leads to decreased production of α -ketoglutarate, a direct product of Krebs cycle, which may also promote HIF-1 α activation because it is a cofactor for the prolyl hydroxylation reaction that degrades HIF-1 α [58]. In a study by Michelakis et al, administration of dichloroacetate, a drug that forces pyruvate to enter Krebs cycle significantly inhibited glioma and is in clinical trial [61]. Both in vivo and in vitro, Dichloroacetate inhibited HIF-1 α as well as suppressed angiogenesis.

Tumor blood flow not only varies spatially and temporally during tumor growth but it also changes according to the state of its angioarchitecture [62]. It is particularly true for vessels that are within the inner mass of the tumor, where the vessels are chaotic and sinusoidal in

appearance and the blood flow is non-laminar and may even be stagnant in some part of its course [63]. Hypoxia induced expression of HIF-1 α leads to increase expansion [64] and tumorigenic potential [65] of CD133⁺ glioma stem cells which could lead to increased tumor derived neo-angiogenesis [52,53]. The expression of HIF-1 α and VEGF are relatively robust in the region of relative hypoxia and in the presence of Angiopoietin-2, they signal endothelial proliferation, basal laminar fragmentation, and facilitate sprouting [65,66]. Angiopoietin-1 recruits perivascular/mural cells, which stabilizes nascent vessels and maintains their integrity; however, the expression of Angiopoietin-1 changes during the course of tumor expansion. The exact etiology of the preferential spatial/ temporal expression of these factors remains unclear. This altering expression could potentially be the cause of involution and dysmorphic transformation of the neovascular tree. The hostile microenvironment with low pH, low partial O₂ pressure and necrotic tissue sustains tumor progression and potentially drug resistance. It is particular true in the "older" central core of the tumor [4,67], a region routinely associated with tumor necrosis. It is plausible that the confounding effects of low oxygen tension combined with dysmorphic vascular tree favors cancer stem cells differentiation as opposed to cancer stem cell renewal.

Cancer stem cells cultured in the presence of vascular endothelial cells showed a five-fold increase in growth as well as maintenance of aggregated tumor spheres and self-renewal capacity [15]. These features were absent in those cells cultured without endothelial cells or their associated signaling factors. In vivo, cells that are associated with the cancer stem cell niche, influence the fate of all neighboring cell types including naïve neuronal cells. The multi-directional regulatory process within this angio-architecture is orchestrated by stem cell related trophic and angiogenic factors such as members of the Wnt, Sonic Hedgehog (SHH) and TGF- β family, and also the intercellular physical contact. These contacts interact with anchoring molecules within the ECM such as VCAM-1/VLA-4, fibronectin, heparans, and other integrin [68-71]. ECM receptors such as integrin- α 6 expressed on GBM cancer stem cells promote their maintenance [72]. When these integrins on cancer stem cells are targeted, there is a decrease in self-renewal, proliferation and tumor forming capacity. Indeed cilengitide, an inhibitor of integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ (which are in clinical trials) have shown good response in preclinical trials [73]. Additionally, some of the factors and proteins sequestered within the cellular matrix are liberated by the proteinases and trigger intracellular changes via their surface signal transduction pathways. Glioma perivascular niche may thus offer a therapeutic target, especially VEGF secreted by endothelial cells as well as integrins expressed by glioma stem cells.

Growth factors and signaling pathways that affecting vascular proliferation and arborization of the vascular tree: Cancer stem cells secrete a multitude of chemokines and growth factors that induce changes in local tumor stroma including the recruitment and proliferation of BM-derived cells to support new vessel development. Notably, VEGF is the most studied factor and is responsible for the coordination of new vessel formation and vascular maintenance. It plays an autocrine and paracrine role within this niche. Additionally, cancer cells may also secrete placental growth factor (PlGF), which promotes adult vasculogenesis by enhancing EPC recruitment and vessel formation at the site of tumor neovascularization [74].

Another characteristic of cancer stem cells is their ability to migrate and infiltrate the surrounding normal tissue. Cancer stem cells acquire mobility by undergo Epithelial-mesenchymal transition (EMT). EMT is usually restricted to embryonic development and tissue repair. The activation of this process is crucial for invasive growth and metastasis. Induction of EMT in cancer cells is achieved by a combination of stromal factors, such as HGF, TGF β , tumor necrosis factor- α and MMPs, and by activating mutations in the RAS proto-oncogene [75-77]. The expression of VEGFA and MMPs, are regulated by hypoxia and pro-inflammatory cytokines. MMPs via their protease activity are required for the degradation of the cellular matrix, a

prerequisite for vessel sprouting.

The other set of signaling pathways important in this process include signaling proteins activated via TGF and EGF receptors. Signal transducer and activator of transcription3 (STAT3) promotes both wound repair and carcinogenesis [78]. Mice that express a constitutively active form of STAT3 in the epidermis develop skin cancer with a shorter latency; the number and malignancy of the tumors were also increased. STAT3 suppresses re-epithelization thus creating a persistent inflammatory state that resembles a chronic wound and a permissible milieu for tumorigenesis [79]. Re-epithelialization terminates neo-angiogenesis, prunes and normalizes the neoangiomatic arcs within the granulating tissue, resulting in decreased influx of cells and reestablishing a quiescent state. In the case of tumorigenesis it closes the temporal window for cancer stem cells proliferation and initiates tumor involution.

It has been known that STAT-3 is essential for the maintenance of an undifferentiated embryonic stem cells pool and the pluripotency of its constituent cells [80]. The importance of STAT-3 has also been addressed in glioblastoma stem cells (GBM-SC). Small molecule inhibitors (STA-21 and S31-201) or short hairpin RNA reduce GBM-SC proliferation and neurosphere formation [81]. It is noteworthy that PTEN negatively regulates STAT-3 and mTOR resulting in stem cells/cancer stem cells quiescence, and PTEN is mutated or deleted in 44% and 60% of GBM patients respectively [82,83]. Hence dysregulation of STAT-3 may be an important event in activation of cancer stem cells.

In the past, Osetopontin has been seen as an important player in the regulation of stem cell renewal particularly at the stem cell niche, it is a negative regulator in the stem cells niche where it helps to limit the size of the stem cell pool [84]. However, the expression of this extracellular matrix associate protein has been linked to tumor progression and metastasis of breast and other solid tumor including GBM. The casual relation of this process relies on the activity of $\alpha_v\beta_3$ integrin mediated Janus Kinase 2 (JAK-2) phosphorylation [85]. Paradoxically, Osetopontin deregulates stem cells/cancer stem cell quiescence by increased phosphorylation of STAT-3 in an environment where excess $\alpha_v\beta_3$ is available. This frees the cancer stem cells from the regulatory restraint imposed by terminal differentiation. This equilibrium with the vascular niche determines the direction of tumor progression or tumor involvement or quiescence.

The function of cancer stem cell vascular niche complexes and future direction

The cancer stem cells theory of tumorigenesis is intertwined with the theory of dormancy of cancer. Recent study has postulated that cancer cells are under constant scrutiny by the immune system [86]. For cancer stem cells, quiescence might be a protective response to a microenvironment that is hostile to its survival and lacks tumorigenic recruitment signals. It has been shown that immuno-editing can promote epithelial-mesenchymal transition and favor cancer stem cells [87]. The decisive force that propels cancer stem cells to achieve a higher degree of autonomy within the niche remains unclear. It is unlikely to be an isolated stochastic event, rather an integration of multiple random events that are closely linked chronologically which ignites the angiogenic switch and the maturation of the vascular elements. The influx of foreign cells such as circulating monocytic cells and vascular progenitors along with the factors expressed by these cells may have fueled epigenetic changes in the naive cells and altered the cellular matrix (Figure 2). The possibility of aberrant signaling events induced by an altered micro-environment, leading to reversible epigenetic changes in each cell type, underscores the heterogeneity within the developing tumor [88]. This allows abrupt changes in the phenotypic expression of the cancer cells, overwhelming the immuno-surveillance and immuno-

suppression. It also confers mobility of the cells to prepare for invasion and distant metastasis. Since these epigenetic changes are reversible they may not be easily recognizable in the final tumor. Other factors that may play a pivotal role in this process are loss of contact inhibition, the rise in hypoxic gradient, and increase in interstitial tension within the niche. All of these processes are intimately linked to further epigenetic alternation and play an important role in malignant transformation resulting in quasi-malignant phenotypes.

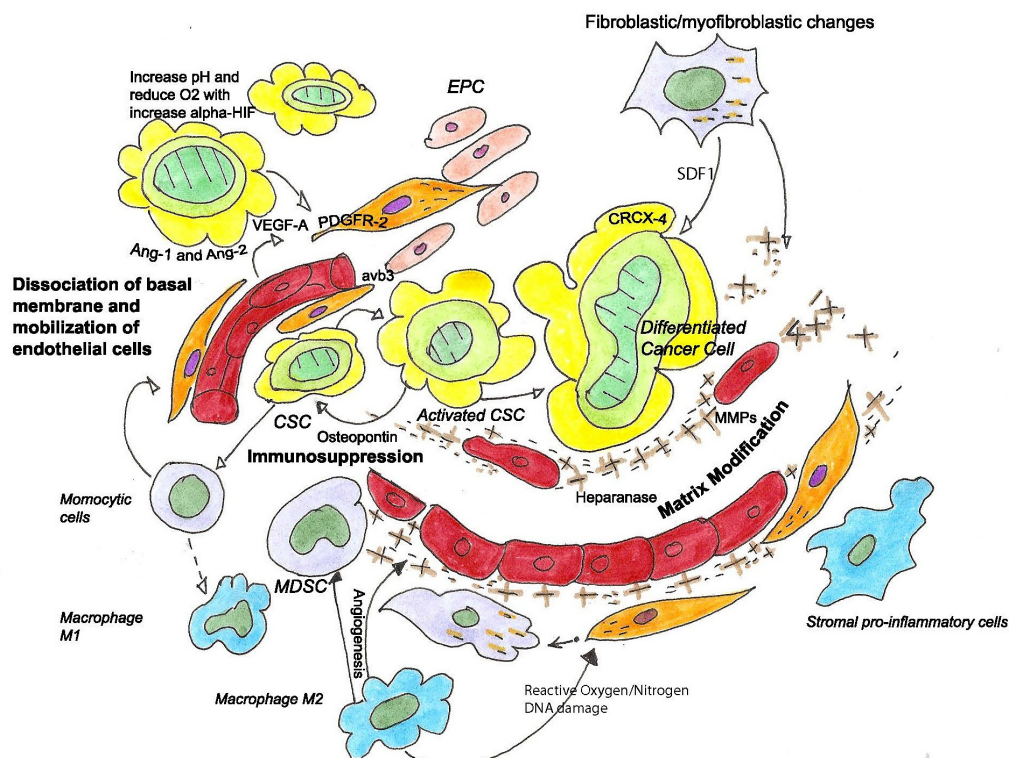


FIGURE 2: Glioma stem cells and vascular niche milieu

Tumor core are in hypoxic states that causes the increase of HIF1 α . This increase in transcription factor HIF1 α leads to increased VEGF expression with a consequent increase in endothelial cells and neoangiogenesis. This is aided by the dissociation of the basal lamina via overexpression of MMP and heparanase. This breakdown causes endothelial cells to generate nascent vascular cords that differentiate to functional vasculature. The increased in M2 macrophage leads to increased reactive oxygen and nitrogen species perpetuating the inflammatory process. The migration and differentiation of cancer stem cells to cancer cells is aided by the action of SDF1 released by the fibroblasts that are associated with the tumor.

It is clear that brain tumors especially gliomas are highly dependent on angiogenesis for their growth. This provides an overwhelming rationale for anti-angiogenic approaches for treating these deadly tumors. Recent studies have suggested that anti-angiogenic therapy may indeed be necessary to "normalize" the glioma vasculature for antitumor agents to reach an effective concentration. Most of these agents target the VEGF or PDGF ligand/receptor interaction that target both cancer cells and endothelial cells. Increased doses of anti-angiogenic agents currently in trial could produce complete tumor regression, but such doses are accompanied with immense side effects. Several agents targeting angiogenesis have been approved for use in non-CNS tumor. Multiple drugs are in various stages of trials in glioma and other CNS tumors (Table 2).

Agent	Phase	Target
2ME2	Phase II	Inhibits HIF-1a
Cediranib	Phase II	VEGFR and PDGFR inhibitor
Pazopanib	Phase II	VEGFR and PDGFR inhibitor
PTC299	Phase II	Inhibits VEGF at the post-transcriptionally
Sorafenib	Phase I/II	VEGFR, PDGFR and BRAF inhibitor
Sunitinib	Phase II	VEGFR and PDGFR inhibitor
Tandutinib	Phase II	Inhibits PDGFR
Vandetanib	Phase I/II	Inhibits VEGFR and EGFR
Vatalanib	Phase I/II	VEGFR and PDGFR inhibitor
ABT510	Phase II	Inhibits CD36 receptor
Aflibercept	Phase I/II	Decoy receptor for VEGF
ATN161	Phase II	Peptide inhibits integrin $\alpha 5\beta 1$
Bevacizumab	Phase II/III	Monoclonal antibody binds to VEGF
Cilengitide	Phase II/III	RGD synthetic peptide inhibits integrin $\alpha v\beta 3$ and $\alpha v\beta 5$
CT322	Phase I	Fibronectin based VEGFR inhibitor
Interferon Alfa 2b	Phase II	Inhibits angiogenesis
TM601	Phase I	Peptide binds to Annexin A2

TABLE 2: Antiangiogenic agents currently at various stages of clinical trial for glioma (peptide/proteins are marked in shaded boxes)

Conclusions

A vascular niche complex is a permissible environment in which the cellular and humoral elements that support repair and remodeling of healthy tissue have gone disarray. As in wound healing and tissue repair, the side population of tissue stem cells and its associated cells are activated; aided by the influxes of vascular progenitors and inflammatory cells, they rebuild and remodel the injury site and restore normal tissue architecture. In tumorigenesis, the activation and the formation of the cancer stem cells-vascular niche complex is the corollary of having a chance event in which a stem cell with deleterious mutation takes root in an epigenetically corrupted niche. The formation of this permissible milieu is the pre-requisition for cancer stem cells to achieve their malignant potential.

Tumor angiogenesis has long been the target in therapeutic designs; numerous strategies have been formulated to disrupt its formation. With the concept of Cancer stem cell vascular niche

complex, it may be more beneficial in finding way to "normalize" this milieu by putting more emphasis on the supportive cells and the matrix.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Author Contribution: HB and VT prepared the manuscript.

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