Angiogenesis in Gliomas

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Mujeeburahim Cheerathodi and Joseph H. McCarty

Abstract

Malignant brain tumors, including *glioblastoma* (GBM), display growth, survival, and invasive properties that are coupled to blood vessels and vascular-derived factors. For example, GBM stem cells (GSCs) home to perivascular niches and invasive tumor cells commonly disperse through the brain microenvironment via extracellular matrix (ECM)-rich vascular basement membranes. Anti-vascular agents that target angiogenesis, and particularly those involving vascular endothelial cell growth factor-A (VEGF-A) and its receptors, improve progression-free survival in GBM patients. However, these benefits are often transient due to compensation by alternative angiogenic pathways. The detailed molecular mechanisms that couple GBM cells to blood vessels during tumor growth and progression as well as following anti-angiogenesis therapies are just beginning to be elucidated, with various cytokines, growth factors, and ECM proteins playing important roles. In this review we will highlight molecular pathways that link cerebral blood vessels and GBM cells during tumor growth, progression, and invasion. We will also discuss mechanisms underlying GBM-induced angiogenesis, with a particular focus placed on roles for integrin adhesion receptors and their ECM protein ligands. Therapies that target angiogenesis in GBM and other brain cancers will also be summarized.

Keywords

Brain cancer • *Glioblastoma* • Growth factors • Integrins • Extracellular matrix • Invasion • Neurovascular unit • Vascular niches

M. Cheerathodi • J.H. McCarty (✉)
Department of Neurosurgery, Unit 1004 S5.8136c, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA
e-mail: jhmccarty@mdanderson.org

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Abbreviations

BBB	Blood–brain barrier
CNS	Central nervous system
EC	Endothelial cell
ECM	Extracellular matrix
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
GBM	*Glioblastoma*
GSC	GBM stem cell
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MMP	Matrix metalloproteinase
MRP	Multidrug resistance protein
PDGF	Platelet-derived growth factor
RTK	Receptor tyrosine kinase
TGFβ	Transforming growth factor β
TIMP	Tissue inhibitors of matrix metalloproteinase
VEGF	Vascular endothelial cell growth factor

7.1 Introduction

The formation of new blood vessels via endothelial cell (EC) proliferation and sprouting, or angiogenesis, is essential for proper development and physiology of all mammalian organs (Adams and Alitalo 2007; Potente et al. 2011). This is particularly relevant in the central nervous system (CNS)—comprised of the brain, spinal cord, and retina—where neurons and glia regulate EC behaviors via direct cell–cell contacts as well as secreted growth factors and extracellular matrix (ECM) proteins (McCarty 2009a; Zacchigna et al. 2008). Aberrant regulation of angiogenesis occurs in various diseases including brain cancers such as gliomas (Bao et al. 2006; Calabrese et al. 2007; Gilbertson and Gutmann 2007). Hallmark features of malignant gliomas include pathological neovascularization, disruption of the intratumoral blood–brain barrier (BBB), and perivascular tumor cell dispersal (Gilbertson and Rich 2007; Jain et al. 2007a; Louis 2006). Gliomas afflict approximately 20,000 people within the United States each year (Holland 2001; Maher et al. 2001; Ohgaki 2005). They represent the most common type of primary brain tumors, and in their advanced stages they are one of the deadliest forms of cancer. Most high-grade gliomas are refractory to standard surgical, radiation, and chemotherapeutic interventions (Ware et al. 2003). Survival rates have changed little in the last few decades, with nearly 100 % of patients succumbing to the disease within 3 years after diagnosis. Hence, understanding the basic cellular and

molecular pathways that contribute to glioma growth and invasiveness may lead to new therapeutic strategies to treat or prevent the pathogenesis of this insidious disease.

Gliomas can be subdivided into three major categories based on their histology and prognosis: astrocytomas, oligodendrogliomas, and ependymomas. Astrocytomas, or gliomas of presumptive astrocytic origin, can be further divided into four main grades (Ware et al. 2003). Grade I pilocytic astrocytomas develop mostly in young adults and are managed primarily via surgical interventions. Grade II astrocytomas are gliomas consisting of differentiated and invasive tumor cells. Grade III anaplastic astrocytoma and grade IV GBMs are poorly differentiated and highly infiltrative tumors (Louis 2006).

Multiple chromosomal abnormalities and gene expression defects have been identified in gliomas, and these alterations often correlate with histological grade and clinical prognosis (Ohgaki 2005; Phillips et al. 2006). In general, glioma initiation and progression involve gene mutations that (1) deregulate growth factor receptor tyrosine kinase signaling and (2) alter the cell cycle checkpoint machinery. Low-grade tumors often express high levels of the growth factors FGF2 and PDGF, as well as their cognate receptor tyrosine kinases (Holland 2001; Shih et al. 2004). Elevated receptor activation in turn leads to amplification of downstream signaling events, often involving Ras (Ding et al. 2001; Holland et al. 2000), and commonly correlates with loss of p53 tumor suppressor functions (Reilly et al. 2000). Disruption of the cell cycle regulatory network is linked to the progression of high-grade gliomas (Holland et al. 1998b; Uhrbom et al. 2002). For example, anaplastic astrocytomas often contain deletions of the tumor suppressors Ink4a/Arf and retinoblastoma (Rb) (Bachoo et al. 2004; Xiao et al. 2002). GBMs also commonly display amplification of EGFR signaling, which can lead to Ras hyperactivation (Holland et al. 1998a). Collectively, these alterations disrupt multiple intracellular signaling pathways that contribute to the progression of glioma from low grade to high grade (Wechsler-Reya and Scott 2001).

The genetic mutations that contribute to gliomagenesis are commonly mutated in other cancers. Thus, glioma progression is likely influenced by a combination of tumor cell-extrinsic factors (Fukumura et al. 2001; Winkler et al. 2004), as well as alterations in a distinct tumor-initiating cell of origin (Sanai et al. 2005; Shih and Holland 2004; Wechsler-Reya and Scott 2001). The exact cell type that gives rise to glioma remains uncertain. However, most neural cells in the adult brain are terminally differentiated. Thus, the tumor-initiating cell of origin for glioma is limited to those compartments that retain proliferative potential, i.e., neural stem cells, glial progenitors, and differentiated glia. Genetically engineered mouse models reveal that astrocytomas arise from presumptive neural stem cells (Alcantara Llaguno et al. 2009; Zheng et al. 2008) and/or oligodendroglial cells (Liu et al. 2011). These cells reside in various regions of the adult brain (Gilbertson and Gutmann 2007), and abnormal regulation of their proliferative and differentiative capabilities likely triggers glioma onset and progression (Aboody et al. 2000; Fomchenko and Holland 2006; Maher et al. 2001).

Most brain tumors, and particularly GBM, harbor a subpopulation of proliferative and multipotent tumor-initiating cells, or GSCs (Dirks 2006). GSCs have several similarities with nonmalignant neural stem cells, including expression of common molecular markers, for example, Nestin and CD133/Prominin-1 (Read et al. 2006). Neural stem cells and brain tumor stem cells also intimately associate with vascular basement membranes in vascular niches. Importantly, contact and communication events between brain tumor stem cells and angiogenic blood vessels positively regulate tumor growth and progression (Bao et al. 2006; Calabrese et al. 2007; Salmaggi et al. 2006). Recently, subpopulations of GBM cells have been shown to transdifferentiate to ECs and pericytes and contribute to vascular pathologies. These events are also influenced by cues within the microenvironment (Ricci-Vitiani et al. 2011; Soda et al. 2011b; Wang et al. 2011) although their pathophysiological significance remains to be determined (Rodriguez et al. 2012). The focus of this review is to highlight how glioma-derived growth factors and adhesion proteins impact angiogenesis in the brain tumor microenvironment.

7.2 Blood Vessel Pathologies in Glioma

Malignant gliomas are defined, in part, by the development of hallmark angiogenesis pathologies including florid microvascular cell proliferation leading to the formation of capillaries with glomeruloid-like tufts (Fischer et al. 2005; Jain et al. 2007b). These abnormal blood vessel morphologies are accompanied by enhanced vascular permeability due to loss of the intratumoral BBB (Jansen et al. 2004; Lopes 2003; Rong et al. 2006). Although traditionally defined as the tight junctions between ECs, the BBB is now considered just one component of a larger multicellular complex, or neurovascular unit (NVU) (Abbott et al. 2006), consisting of neurons and astrocytes, vascular ECs and pericytes, as well as various growth factors and extracellular matrix (ECM) proteins in vascular basement membranes (McCarty 2009b). Comprised mainly of EC tight junctions and multidrug resistance transporters, the BBB regulates the exchange of ions, molecules, and cells between the circulation and brain and is an impediment for drug delivery (Liebner et al. 2011; Pardridge 2002). The molecular mechanisms that control BBB development and physiology remain largely unknown, although Wnts (Daneman et al. 2009; Liebner et al. 2008; Stenman et al. 2008), G protein coupled receptors such as Gpr124 (Anderson et al. 2011; Cullen et al. 2011; Kuhnert et al. 2010), and integrin-activated TGFβs (McCarty et al. 2005; Proctor et al. 2005) play important roles as detailed below.

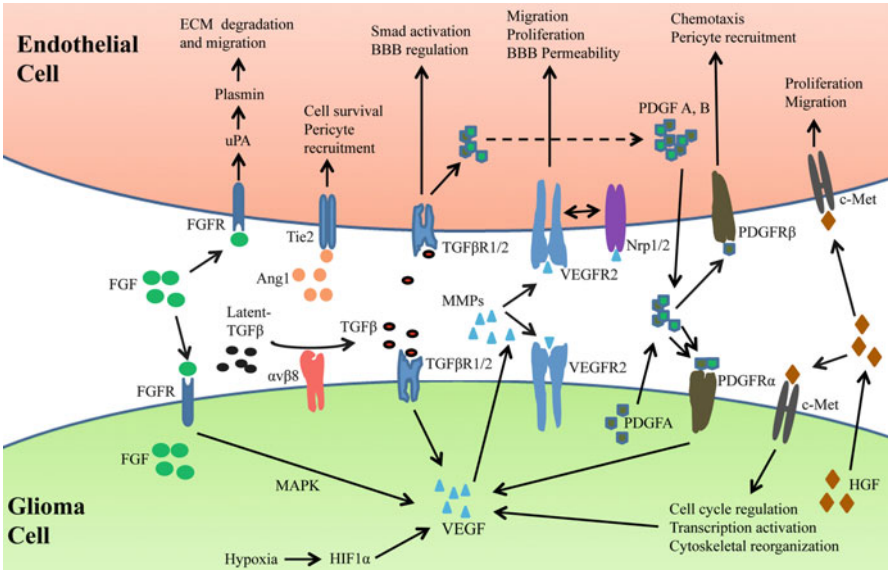

Fig. 7.1 A summary of factors involved in glioma exploitation of angiogenesis. Glioma cells dynamically communicate with blood vessels via various secreted growth factors and ECM proteins. These factors control cerebral endothelial cell and pericyte survival, proliferation, and BBB permeability

7.3 Growth Factors and Cell Adhesion Molecules in Glioma Angiogenesis

A balance between angiogenic activators and inhibitors regulates blood vessel growth, stability, and permeability (Hanahan and Folkman 1996). In glioma, this balance is disrupted by a number of pro-angiogenic and anti-angiogenic factors. Below we will discuss various growth factors and cell adhesion proteins that control angiogenesis during glioma initiation and progression (Fig. 7.1).

7.3.1 VEGF

Vascular endothelial cell growth factor-A (VEGF-A) is a critical regulator of angiogenesis during organ development as well as tumor growth and progression. VEGF-A was first discovered by Dvorak and colleagues who initially named it vascular permeability factor for its ability to enhance permeability properties of blood vessels (Dvorak 2006). Efforts by Ferrara and colleagues revealed that VEGF-A also regulates vascular EC proliferation, migration, and survival (Leung et al. 1989). Subsequent studies by a number of independent groups identified a larger gene family consisting of at least six different VEGF family members

(Jansen et al. 2004). VEGF genes express multiple protein isoforms and each can bind to distinct or shared transmembrane receptor tyrosine kinases including VEGFR1, VEGFR2, and VEGFR3 as well as Neuropilins (Bielenberg et al. 2006). These receptors are also expressed in glioma cells, suggesting autocrine VEGF signaling pathways (Ellis and Hicklin 2008).

VEGF-A expression is upregulated in glioma cells and this correlates with tumor growth and malignancy (Bulnes et al. 2012). Hypoxia-inducible factor 1a (HIF1α) is one of the major transcription factors that regulate VEGF-A gene expression (Kaelin and Ratcliffe 2008; Semenza 2003). In addition to HIF1α, other transcription factors also bind to the VEGF-A promoter to regulate gene expression. For example, p53 and VHL tumor suppressors form complexes with SP1 transcription factors and inhibit VEGF transcription (Kargiotis et al. 2006; Mukhopadhyay et al. 1997). p53 is commonly deleted in high-grade gliomas (Verhaak et al. 2010). EGFR signaling, which is often amplified in gliomas, also regulates VEGF-A expression via activation of the MAPK/ERK pathway (Woods et al. 2002). These effects were nullified by the inhibition using anti-EGFR antibodies (Goldman et al. 1993; Okamura et al. 1992; Valter et al. 1999). In addition, a truncated and constitutively active form of EGFR, EGFRvIII, has been shown to upregulate VEGF expression in glioma cells via Ras-dependent mechanisms (Feldkamp et al. 1999).

7.3.2 Notch/Delta

Cross talk between the VEGF-A and Notch pathways coordinately regulates blood vessel growth and stability (Chappell et al. 2009; Jakobsson et al. 2010). For example, VEGF-A stimulates Notch 1 expression which induces the formation of specialized endothelial "tip cells" found at the leading front of sprouting blood vessels (Hellstrom et al. 2007a). VEGFR2 signaling and tip cell formation are dampened by the anti-angiogenic Notch ligand Dll4 (Hellstrom et al. 2007b; Noguera-Troise et al. 2006). Deletion of one Dll4 allele or blockade of Notch activation with γ-secretase inhibitors induces similar phenotypes including hyperactive tip cell formation (Hellstrom et al. 2007b; Noguera-Troise et al. 2006; Siekmann and Lawson 2007). In contrast, Jag1 is a pro-angiogenic Notch ligand that counterbalances Dll4-Notch signaling and stimulates tip cell formation (Benedito et al. 2009). Exploitation of Jag1 by cancer cells has been reported; for example, epithelial carcinoma cells overexpress Jag1 and activate Notch in ECs (Zeng et al. 2005). Additionally, Jag1 in metastatic breast cancer cells mediates interactions with Notch in osteoblasts of the bone microenvironment (Sethi et al. 2011). Lastly, Notch signaling pathways are often hyperactivated in GBM (Fan et al. 2010; Hambardzumyan et al. 2008; Stockhausen et al. 2010). Inhibition of Notch activation diminishes mouse and human GSC self-renewal (Fan et al. 2010; Jeon et al. 2008) and can synergize with temozolomide to reduce glioma growth in xenograft models (Gilbert et al. 2010).

7.3.3 FGFs

Fibroblast growth factors (FGFs) are a family of structurally related proteins that regulate a wide range of developmental and pathophysiological processes (Friesel and Maciag 1995). Among the nine FGF family members, FGF-1 and FGF-2 are well characterized as angiogenic mediators and are often overexpressed in gliomas. FGF signaling has also been reported to promote VEGF expression in glioma cells (Friesel and Maciag 1995; Stefanik et al. 1991; Tsai et al. 1995). Degradation of ECM is an important step in blood vessel sprouting. FGF-2 facilitates EC migration through the ECM by upregulating urokinase-type plasminogen activator (uPA), which activates plasmin, a protease for many ECM protein components (Dunn et al. 2000).

7.3.4 PDGFs

Members of the platelet-derived growth factor (PDGF) family signal through different receptor tyrosine kinases (PDGFRs). Receptor binding activates multiple kinase cascades including PI3kinase, MAPK, JAK, SRC, and phospholipase C gamma (Fomchenko and Holland 2007). Gliomas express high levels of PDGFA and PDGFRα, but the tumor vasculature expresses low levels of PDGFRα. Instead, many glioma blood vessels express robust levels of PDGFRβ. These data suggest PDGFRα-dependent autocrine/paracrine signaling mechanisms in tumor cells and PDGFRβ-dependent paracrine signaling in ECs and pericytes (Hermanson et al. 1992). To study the effects of PDGFB in brain tumorigenesis, a mouse model was generated by overexpressing PDGFRβ in glial cells (Hermanson et al. 1992). These transgenic mice do not develop spontaneous tumors and showed normal brain development. However, when crossed to a p53−/− background mice developed tumors with pathologies similar to human GBMs including pseudopalisading necrosis, glomeruloid vessels, and BBB breakdown. Interestingly, overexpression of PDGFA in neurogenic regions of the adult mouse brain leads to premalignant gliomas via uncontrolled proliferation of neural stem and progenitor cells (Jackson et al. 2006). Interestingly, PDGFA is also a molecular marker for the classical GBM subtype (Verhaak et al. 2010). Using in vitro models, PDGFB was found to induce chemotaxis of rat brain microvascular ECs verifying the direct action of PDGFs during angiogenesis. PDGFs did not induce migratory effects on glioma cells, but were chemotactic for ECs (Brockmann et al. 2003).

7.3.5 TGFβs

The TGFβ superfamily of cytokines consists of bone morphogenetic proteins, Mullerian inhibiting substance, and activins. These proteins are involved in regulating a number of cellular processes ranging from proliferation to apoptosis (Massague et al. 2000). Members of the TGFβ family (TGFβ 1, 2, and 3) signal via

canonical receptor serine/threonine kinases, TGFβR2 and TGFβR1. TGFβR2 is shared by all ligands and dimerizes with different TGFβR1s to form signaling-competent receptor complexes. Endoglin is a TGFβ co-receptor that facilitates ligand presentation to TGFβR1/TGFβR2 heterodimers (Massague and Gomis 2006). Immunohistochemical analysis of gliomas has shown upregulation of TGFβ as well as TGFβR1 and TGFβR2. TGFβ signaling via Smad transcription factors, or canonical TGFβ signaling, is also hyperactivated in many high-grade gliomas likely via uncontrolled growth and differentiation of GSCs (Bruna et al. 2007; Penuelas et al. 2009).

TGFβs often inhibit proliferation by cell cycle arrest in the G1 phase and this is mediated by regulation of INK4B expression. Interestingly, at higher TGFβ concentrations these growth inhibitory effects are negligible or in some cases potentiate glioma cell proliferation, in part owing to loss of p15 and p16 (Jen et al. 1994; Rich et al. 1999). The effects of TGFβs on angiogenesis remain controversial. In vitro studies using bovine aortic ECs treated with TGFβs showed an inhibitory effect while in vivo studies using angiogenesis system showed pro-angiogenic effects (Fajardo et al. 1996; Frater-Schroder et al. 1986). Ablation of TGFβ receptors in ECs leads to early lethality due to impaired yolk sac angiogenesis and cardiovascular development (Carvalho et al. 2007; Park et al. 2008). Additionally, TGFβ can stimulate VEGF production in glioma cells and pharmacological inhibition of TGFβR1 leads to decreased expression of VEGF and plasminogen activator inhibitor-1 (PAI-1) in gliomas (Hjelmeland et al. 2004; Koochekpour et al. 1996). PDGFA and PDGFB are downstream effectors of TGFβ in ECs while PDGFRβ expression is upregulated in vascular smooth muscle cells (Dunn et al. 2000; Helseth et al. 1988).

7.3.6 Angiopoietins

Angiopoietins (Ang1 and Ang2) play essential roles in regulating blood vessel development and stability. During embryogenesis Ang1 binds to its receptor tyrosine kinase, Tie2, and regulates stability of pericyte–EC interactions (Suri et al. 1996). Tumor cells also express Ang1, but Ang2 expression is generally limited to activated endothelium (Augustin et al. 2009). Ang2 competes with Ang1 for Tie2 binding and antagonizes Ang1 signaling (Maisonpierre et al. 1997). Hypoxia induces Ang2 expression in ECs, which disrupts Ang1–Tie2 signaling probably by acting as an antagonist to Ang1 (Holash et al. 1999). Antagonists that inhibit angiopoietin interactions with Tie receptors are currently being tested in clinical trials as anti-angiogenic agents (Peeters et al. 2013).

7.3.7 HGF

Scatter factor/hepatocyte growth factor (SF/HGF) signaling plays versatile roles in physiological and pathological processes including organogenesis and cancer

(Abounader and Laterra 2005; Birchmeier and Gherardi 1998). SF/HGF and its receptor tyrosine kinase, c-Met, are expressed by glioma cells which correlate with malignancy and vascular pathologies (Koochekpour et al. 1997; Moriyama et al. 1998; Rosen et al. 1996). Overexpression of SF/HGF caused increased tumorigenesis and tumor angiogenesis while inhibition of c-Met signaling using blocking antibodies or siRNAs suppresses tumor growth (Abounader et al. 1999, 2002; Laterra et al. 1997). In addition to glioma cells, c-Met is also expressed in tumor-associated blood vessels suggesting paracrine signals from tumor cells lead to EC growth and sprouting (Ding et al. 2003; Nakamura et al. 1995).

HGF contributes to degradation of vascular basement membranes and promotes EC migration by upregulating expression of MMPs such as MT1-MMP, MMP2, and urokinase. Another possible way SF/HGF contributes to tumor angiogenesis is by promoting proliferation through MAPK/Stat3 pathway and inhibiting apoptosis of tumor ECs (Lamszus et al. 1998; Ma et al. 2002; Wang et al. 2004). In Matrigel assays using human umbilical vein ECs, SF/HGF induces EC tube formation in a dose-dependent manner. This effect was abolished by treating with anti-HGF antibodies. In another experiment when ECs and SF/HGF secreting keratinocytes were cocultured in an in vitro system it led to the formation of EC tubes (Jiang et al. 1999; Martin et al. 1999; Wojta et al. 1999).

7.3.8 IL-6 and IL-8

Interleukins are cytokines secreted by normal and tumor cells, and in gliomas they promote proliferation and directional migration (Brat et al. 2005). Many glioma cells are capable of secreting IL-6, which can activate Sp1 and Sp3 transcription factors to induce expression of VEGF-A mRNA. IL-8 is also expressed at high levels in many glioma cells (Van Meir et al. 1990, 1992). IL-8 is a potent mediator of tumor angiogenesis via its cell surface receptors CXCR1, CXCR2, and DARC (Holmes et al. 1991; Murphy and Tiffany 1991). Glioma cells express all three receptors while DARC, but not CXCR1 and CXCR2, is expressed in microvascular ECs. CXCR1 and CXCR2 are expressed in perivascular leukocytes; hence, the angiogenic properties of IL-8 involve inflammatory responses as well. Lastly, under hypoxic conditions, IL-8 expression is upregulated via Ap-1 binding to IL-8 promoter sequences (Brat et al. 2005; Desbaillets et al. 1997, 1999).

7.3.9 TNFα

Tumor necrosis factor alpha (TNFα) is a macrophage-derived cytokine that has pleiotropic effect on cells. At low concentrations TNFα is pro-angiogenic while at high concentrations it displays anti-angiogenic activities (Fajardo et al. 1992). In high-grade gliomas, TNFα is expressed in multiple cell types including tumor cells and ECs (Maruno et al. 1997), while its receptors are expressed by ECs (Slowik et al. 1993). Angiogenic effects of TNFα are mediated indirectly by inducing

expression of a number of other pro-angiogenic molecules. For example, upon TNFα treatment VEGF-A expression is upregulated in glioma cells. TNFα also upregulates expression of VEGF, IL-8, and FGFs in human microvascular ECs in vitro and blocking antibodies directed against TNFα inhibit these effects (Kargiotis et al. 2006; Ryuto et al. 1996).

7.3.10 Other Pro-angiogenic Factors

Additional growth factors and cytokines play important yet less characterized roles in angiogenesis. For example, the inducible early response gene product Cyr61/CNN1 and connective tissue growth factor CTGF/CNN2 are growth factors belonging to CNN family that induce proliferative effects on glioma cells and are downstream targets of c-Met (Goodwin et al. 2010; Jedsadayanmata et al. 1999). Expression of these proteins correlates with glioma malignancy. Tumor-associated ECs also express CTGF, suggesting pro-angiogenic roles (Pan et al. 2002; Xie et al. 2004).

The cytokine stromal cell-derived factor 1 (SDF-1/CXCL12) and its chemokine receptor CXCR4 regulate glioma cell migration and tumor cell homing to blood vessels (Rao et al. 2012). Immunohistochemical analysis revealed expression and co-localization of SDF-1 and CXCR4 in glioma cells, with an increasing intensity correlating with tumor grade. Expression of these proteins was absent in normal brain (Rempel et al. 2000). This suggests that the SDF-1/CXCR4 signaling axis may be a novel target for inhibiting glioma growth and invasion.

Various signaling effectors that control neural development also play central roles in glioma growth and angiogenesis (Eichmann et al. 2005). For example, semaphorins have important functions in controlling axonal guidance and also regulate angiogenesis. Semaphorins bind to plexin as well as Nr cell surface receptors. Nrps are co-receptors for VEGF-A in ECs and tumor cells and promote cell proliferation. Whereas VEGFR2-dependent angiogenesis results in increased vascular permeability, plexin and Nrp elicit anti-angiogenic effects upon semaphorin binding. Additionally, application of anti-Nrp inhibitory antibodies in preclinical brain tumor models results in suppression of tumor growth (Snuderl et al. 2013). Lastly, Slit-Robo interactions are important regulatory pathways in angiogenesis. Depending on its interacting receptor, Slit has opposing roles in angiogenesis. For example, when Slit binding to Robo1 leads to pro-angiogenic effects, interactions with Robo4 have anti-angiogenic outcomes (Jain et al. 2007a; Tate and Aghi 2009).

7.3.11 Anti-angiogenic Growth Factors and Cytokines

A balance between pro-angiogenic and anti-angiogenic factors, termed the angiogenic switch, controls vessel growth and stability. Alterations in this switch, for example, overexpression of pro-angiogenic factors or diminished expression of

anti-angiogenic factors, promote blood vessel growth and sprouting (Hanahan and Folkman 1996). Below we detail a partial list of anti-angiogenic molecules and their likely roles in regulating glioma angiogenesis.

Angiostatin is a 38 kDa fragment of plasminogen generated by cathepsin D and MMP activities. It was the first anti-angiogenic factor to be identified in mouse models of metastatic cancer (O'Reilly et al. 1994; Tate and Aghi 2009). Angiostatin is a ligand for αvβ3 integrin and downstream signaling leads to apoptosis of ECs and tumor cells (Kirsch et al. 1998; Nishida et al. 2006; Tarui et al. 2001). An angiostatin receptor is NG2, a chondroitin sulfate proteoglycan expressed by pericytes, oligodendrocytes, and tumor cells (Stallcup and Huang 2008). NG2 can bind and sequester angiostatin and impact angiogenesis by altering the angiogenic switch (Chekenya et al. 2002; Chekenya and Pilkington 2002). Another receptor for angiostatin is ATP synthase (Rege et al. 2005). Interactions with angiostatin inhibit the enzymatic activities of ATP synthase and reduce cellular ATP production (Moser et al. 2001). Angiomotin was also identified as an angiostatin binding partner in yeast two-hybrid assays. Angiostatin functions by antagonizing the normal pro-migratory and pro-invasive functions of angiomotin (Rege et al. 2005).

Endostatin is a C-terminal fragment of type XVIII collagen, a basement membrane protein, and is another protein with anti-angiogenic properties. Endostatin induces its effects by binding to fibronectin and α5β1 and αvβ3 integrins and potentially blocking the formation of endothelial focal adhesions (O'Reilly et al. 1997; Rehn et al. 2001; Wickstrom et al. 2002).

Thrombospondins are ECM proteins that induce pro- and anti-angiogenic outcomes. In the aortic ring assay, overexpression of thrombospondins inhibits vascular cell migration and blood vessel sprouting. These effects are mediated through the CLESH domain of the cells surface receptor CD36 and type I repeats of thrombospondins-1 and -2 (Klenotic et al. 2013). Thrombospondin knockout mice also display defective wound healing and tumor-induced angiogenesis (Lawler 2000).

Tissue inhibitors of matrix metalloproteases (TIMPs) negatively regulate MMP enzymatic activities; they control EC proliferation and downregulate expression of VEGF-A. TIMPs also have pro-angiogenic properties owing to their potential to block MMP activities. For example, reduced levels of MMP-dependent expression of angiostatin and endostatin result in anti-tumorigenic and anti-angiogenic properties (Jiang et al. 2002). Lastly, pigment epithelial-derived factor (PEDF) is a member of serpin family of serine proteases that regulate neuronal differentiation and survival and are also negative regulators of angiogenesis. A specific receptor pathway, through which PEDF contributes to anti-angiogenesis, has not revealed but a key pathway involves Fas signaling (Bouck 2002; Rege et al. 2005).

7.4 Integrins in Glioma Angiogenesis

Integrins are αβ heterodimeric receptors for many ECM protein ligands that play central roles in controlling cell growth, migration, and other responses (Hynes 2002). Integrin-ECM affinity is modulated by "inside-out" signaling mechanisms (Kim et al. 2011; Vinogradova et al. 2002) involving proteins such as talins (Calderwood et al. 1999; Tadokoro et al. 2003) and kindlins (Harburger et al. 2009; Ma et al. 2008) that bind to β integrin cytoplasmic domains and induce conformational changes in extracellular regions (Shattil et al. 2010; Takagi et al. 2002; Xiong et al. 2001). ECM adhesion subsequently triggers "outside-in" signaling via adhesion protein complexes and the cytoskeleton (Harburger and Calderwood 2009; Parsons et al. 2010). In vertebrates there are 26 different integrin genes: 18 genes encoding α subunits and 8 β subunit genes. The network of integrin–ligand interactions is vast: some integrins are ligand-specific while others bind many, sharing ligands. This overlap allows for one ECM ligand to have multiple effects on a cell via adhesion to different integrins.

7.5 Integrins in GBM Cells

The brain contains a rich milieu of extracellular matrix (ECM) proteins (Thiery 2003) and abnormal regulation of cell–ECM communication is associated with gliomagenesis (Bellail et al. 2004; Gladson 1999; Shi et al. 2007a); see also Chaps. 10 and 11. For example, glioma cells like nonmalignant neural stem cells migrate through the brain parenchyma along blood vessels and white matter tracts (Sanai et al. 2005). In fact, the infiltrative nature of these tumor cells is an important determinant in the poor prognosis associated with GBM. Most metazoan cells communicate with protein components of the ECM via a family of heterodimeric cell surface receptors known as integrins (Hynes 2002). In addition to their extracellular adhesion functions, integrins also regulate intracellular signal transduction pathways that control multiple cellular responses (Giancotti and Ruoslahti 1999). In vertebrates there are 26 distinct integrin genes: 18 genes encoding α subunits, and 8 genes that encode β subunits (Hynes 2002).

Various integrins and intracellular signaling partners have been linked to the onset and/or progression of glioma (Shi et al. 2007b; Tucker 2006; Uhm et al. 1999a). For example, the fibronectin receptor α5β1 integrin is expressed in human glioma cells and inhibition of α5β1 integrin with specific small molecule antagonists retards glioma cell proliferation (Maglott et al. 2006). Additionally, human glioma cell lines express the laminin receptors α3β1 and α6β1, and these integrins regulate migration on laminin substrates (Uhm et al. 1999b).

The five members of the αv integrin subfamily primarily recognize RGD tripeptide motifs present in many shared ECM ligands, most of which are abundantly expressed in the brain microenvironment. αv integrin ECM ligands include vitronectin and fibronectin (Kalluri 2003), collagen IV (Venstrom and Reichardt 1995), and the latent associated peptide of TGFβ1 (LAP-TGFβ1) (Moses and Serra

1996). Various data link abnormal regulation of αv integrin expression and function to glioma cell growth and invasiveness. For example, αvβ1 integrin expressed in U87 glioma cells binds to the extracellular matrix protein, Ang2, leading to enhanced glioma invasiveness (Hu et al. 2006). More recently, αvβ1 integrin was found to be upregulated in glioma cells treated with anti-vascular agents, with integrin expression promoting angiogenesis and tumor cell invasion (Carbonell et al. 2013; Jahangiri et al. 2013). Human malignant gliomas display elevated levels of αvβ3 and αvβ5 integrins, suggesting that these integrins contribute to glioma cell survival and invasion (Bello et al. 2001; Treasurywala and Berens 1998). Indeed, small molecule inhibitors of αvβ3 integrin reduce glioma growth and invasiveness in vitro and in vivo (Chatterjee et al. 2000). Pieper and colleagues have shown that transformed β3−/− astrocytes form abnormally large intracranial tumors, suggesting that αvβ3 integrin may act to suppress tumor cell growth (Kanamori et al. 2004). More recent studies reveal that αvβ3 integrin exerts opposing effects, depending on whether it is expressed in tumor cells or brain microenvironment (Kanamori et al. 2006).

7.6 αvβ8 in Glioma Angiogenesis and Tumor Cell Invasiveness

The normal brain depends on αvβ8 integrin and its interactions with the ECM. The blood vessels of mice null for αv or β8 dilate, the BBB is compromised, and the mice suffer from severe CNS hemorrhage (McCarty et al. 2002), (Zhu et al. 2002). αvβ8 integrin binds to ECM-associated latent-TGFβ ligands through RGD sites and mediates release of active TGFβs. The ligands then bind the TGFβRI/II and signal through Smads and other pathways resulting in a myriad of effects. In the context of glioma, αvβ8 integrin protein levels are critically important in angiogenesis and invasiveness (Fig. 7.2). Angiogenesis is more severe in tumors with low levels of endogenous β8 integrin and overexpression of the integrin diminishes these angiogenesis pathologies. Glioma cells expressing high endogenous levels of αvβ8 integrin generate less angiogenic tumors, yet the tumors are more invasive. Invasive pathologies can be attenuated by silencing integrin gene expression using lentiviral-delivered shRNAs (Tchaicha et al. 2011). More specifically, changes are detected in cell polarity and directional migration. In scratch-wound assays cells with low levels of β8 integrin had fewer ECM contacts and displayed delayed polarization into the wound region. In contrast, β8 integrin-expressing cells formed organized actin cytoskeletal networks and polarized in a uniform direction toward the wound. αvβ8 integrin control of glioma cell polarity and directional migration is mediated, in part, via binding to RhoGDI1 leading to regulation of the Rho GTPase signaling cascade (Reyes et al. 2013). It has also recently been seen that αvβ8 is negatively regulated by mir-93, leading to gliomas with increased size and neovascularization (Fang et al. 2011).

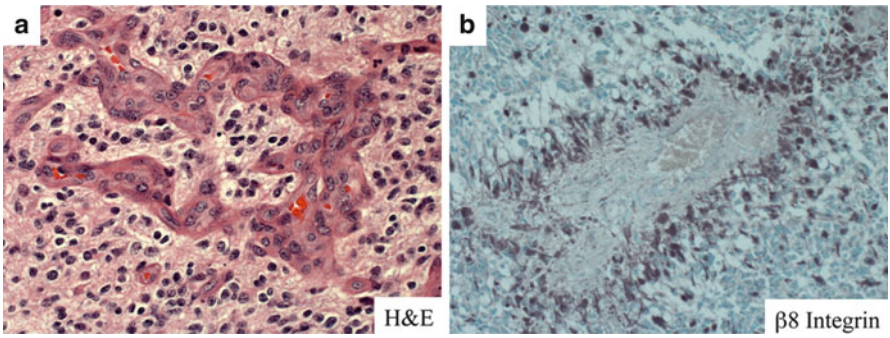

Fig. 7.2 αvβ8 integrin regulation of blood vessel pathologies in glioma. (**a**) A human GBM section stained with hematoxylin and eosin (H&E) revealing distended, glomeruloid-like blood vessels. (**b**) Human GBM section immunostained with antibodies targeting β8 integrin. Note the enrichment of β8 integrin protein expression (*brown stain*) in perivascular tumor cells

7.7 αvβ8 Integrin in Neurovascular Development and Physiology

Neural cells and vascular cells within the brain microenvironment intimately interact and communicate to form multicellular structures, or neurovascular units (Ballabh et al. 2004; Iadecola 2004; McCarty 2005; Zlokovic 2005). Proper cell–cell communication at the neurovascular unit is essential for normal CNS development, and abnormal neurovascular functions are linked to various CNS pathologies (Abbott 2002; Ballabh et al. 2004; McCarty 2005). Cerebral blood vessels are entirely compartmentalized from the surrounding neural microenvironment via a vascular basement membrane that contains a rich assortment of ECM components (Marin-Padilla 1985). Astrocyte end feet associate with the ablumenal surfaces of nearly all cerebral blood vessels via direct contacts with the vascular basement membrane (Abbott 2002). Astrocyte–blood vessel communication plays important roles in regulating molecular transport across the BBB, and also modulates rates of cerebral blood flow in response to local metabolic demands (Begley and Brightman 2003; Engelhardt 2003; Neuwelt 2004; Simard et al. 2003; Zonta et al. 2003). Astrocytes express a variety of cell surface adhesion molecules, including several integrins. At least two integrins, α6β4 and αvβ8, mediate contact and communication between perivascular neural cells and ECM components of the vascular basement membrane (Milner and Campbell 2002).

The αv and β8 integrin subunits are absolutely essential for proper neurovascular development (McCarty et al. 2002, 2005). Mouse embryos completely null for the αv integrin gene, and thus lacking all five αv integrin family members, develop CNS-specific vascular defects that include abnormal angiogenesis and intracerebral hemorrhage (Bader et al. 1998; McCarty et al. 2002, 2005). Similar integrin-dependent phenotypes are detected in the neonatal retina, which is vascularized after birth (Hirota et al. 2011).

The β8 integrin subunit pairs exclusively with αv integrin. To study αvβ8 integrin functions in the postnatal CNS Nestin-Cre transgenic mice were used to ablate αv or β8 integrin gene expression specifically in CNS neural cells. Conditional αv integrin mutants develop embryonic intracerebral hemorrhage that is grossly apparent at birth (McCarty et al. 2005). However, unlike complete αv knockouts, Nestin-Cre conditional mutants live beyond the first day of birth and survive for several months. Using a GFAP-Cre transgene, we also induced hemorrhage in the embryonic and neonatal brain after αv gene ablation (McCarty et al. 2005). Similarly, the β8 integrin gene was selectively ablated in the CNS using an identical Nestin-Cre transgene (Proctor et al. 2005). These animals also develop embryonic and neonatal intracerebral hemorrhage that is phenotypically identical to that observed in the αv integrin mutants. Deletion of the other four αv integrin-associated β subunits does not yield similar CNS vascular phenotypes (Hynes 2002). Genetic ablation of αv or β8 integrin expression in vascular ECs using the Tie2-Cre transgene did not lead to intracerebral hemorrhage or other obvious neurovascular defects (McCarty et al. 2005). These αv and β8 integrin mutant mice actually develop intestinal autoimmunity due to activities of Tie2-Cre in hematopoietic stem cells. Subsequent studies have shown that αvβ8 integrin in dendritic cells regulates latent TGFβ activation and signaling to control intestinal homeostasis.

Collectively, these molecular genetic data prove that αvβ8 integrin in CNS neural cells, particularly astroglia, regulates proper neurovascular development. Loss of αvβ8 integrin expression on CNS glia leads to defective glial-vascular cell adhesion, resulting in abnormal brain angiogenesis and intracerebral hemorrhage. αv conditional mutants also display neurological phenotypes, including sporadic seizures and a rigid gait, and mice generally do not survive beyond 8 postnatal months (McCarty et al. 2005). Similar phenotypes have been reported for the β8 integrin mutants (Proctor et al. 2005), again suggesting that the neurological defects that develop in the αv mutants are due to the specific loss of αvβ8 integrin. Additional postnatal brain deficits in β8 integrin mutant mice include impaired neuronal migration in the rostral migratory stream and widespread perivascular reactive gliosis (Mobley and McCarty 2011; Mobley et al. 2009).

αvβ8 integrin is a receptor for LAP-TGFβ1, and adhesion to an RGD peptide sequence within LAP causes activation of TGFβ signaling pathways in ECs (Cambier et al. 2005; Mu et al. 2002). Genetic ablation of TGFβ receptors in ECs leads to neurovascular phenotypes that are identical to those that develop in Nestin-Cre αv or β8 integrin mutants (Allinson et al. 2012; Arnold et al. 2012; Nguyen et al. 2011). Interestingly, TGFβ1 stimulation of vascular ECs in vitro leads to the upregulation of various ECM proteins, such as thrombospondin-1 and plasminogen activator inhibitor-1, that play established roles in regulating developmental angiogenesis and postnatal neurovascular functions (Del Zoppo 2005; Lawler 2000). Lastly, human genetic data reveal that single nucleotide polymorphisms within the TGFβ1 gene are associated with elevated risk of age-related neurovascular diseases (Kim and Lee 2006). Hyperactivation of TGFβ1-mediated signaling pathways is detected in advanced stages of glioma (Bruna et al. 2007; Rich and Bigner 2004).

Defective TGFβ activation and signaling are linked to various adult-onset CNS vascular pathologies, including Arteriovenous Malformations (Su et al. 2010), Hereditary Hemorrhagic Telangiectasia, and Pulmonary Arterial Hypertension (Orlova et al. 2011). A single nucleotide polymorphism in the TGFβ1 gene is linked to increased susceptibility to stroke (Kim and Lee 2006).

7.8 Anti-angiogenesis Therapies in Glioma

Significant progress has been made in understanding the molecular genetic events that lead to GBM initiation and progression (Furnari et al. 2007). However, only 5 % of the patients with GBM survive 5 years or more, and the medium overall survival time is about 15 months (Stupp et al. 2005; Taylor and Gerstner 2013). In addition to surgical resection, current standard-of-care treatments consist of radiation therapy and temozolomide (Stupp et al. 2005). Since gliomas are such highly vascularized neoplasms, targeting angiogenic pathways was thought to have powerful clinical benefits. Indeed, VEGF-A and VEGFRs, the main regulators of angiogenesis, as well as a number of other pro-angiogenic molecules (see above) are often overexpressed in malignant gliomas.

The US Food and Drug Administration approved the use of the anti-angiogenic antibody Bevacizumab/Avastin for the treatment of colon, lung, and breast cancers. Subsequently, in 2009 Bevacizumab was approved as a monotherapy for the treatment of gliomas (Mrugala et al. 2012). Bevacizumab is a humanized monoclonal antibody directed against VEGF-A but not other VEGF family members (Onishi et al. 2011). This antibody binds to all VEGF-A isoforms and proteolytic fragments with comparable affinities. In gliomas, Bevacizumab treatment gave promising results when combined with irinotecan. The treatments resulted in radiographic response rates of 28–40 % and a 6-month progression-free survival rate of 40–50 %. These efforts led to phase 2 clinical trials, which tested Bevacizumab as a monotherapy or in combination with irinotecan (Friedman et al. 2009; Vredenburgh et al. 2007). Combination therapies resulted in progression-free survival rates of 50.2 %, which was significantly higher than the 35 % response with Bevacizumab monotherapies. However, when compared to the medium overall survival, Bevacizumab showed promise with 9.7 months against 8.9 months in combination therapy, although progression-free survival rates were more pronounced with irinotecan. Overall survival was not significantly improved likely due to combined cytotoxic effects, leading to approval of Bevacizumab as a monotherapy for treating recurrent GBM in the United States (Kreisl et al. 2009; Taylor and Gerstner 2013). A recent publication described two patients displaying responses after receiving a combination treatment of radiation followed by temozolomide and bevacizumab, with ongoing progression-free survival of 37 and 47 months (Aguilera et al. 2013).

However, recent studies have revealed unexpected tumor cell behaviors resulting from Bevacizumab treatment. While Bevacizumab caused a reduction in tumor volumes, 30–50 % of patients developed highly infiltrative growth patterns.

Inhibition of angiogenesis results in a shift in tumor growth properties toward more infiltrative (Norden et al. 2008; Shapiro et al. 2013). Preclinical mouse models showed similar results, with inhibition of VEGF signaling causing U87 satellite lesions to form distal to the primary tumor (de Groot et al. 2010; Lucio-Eterovic et al. 2009). A separate study also yielded similar results with a medium overall survival of 8.9 months (Sahebjam et al. 2013) and other studies showed comparable data (Demirci et al. 2013; Nagane et al. 2012).

7.8.1 Cilengitide

Activation of integrin signaling in concert with growth factor receptor tyrosine kinases regulates a number of cellular processes involved in angiogenesis as well as tumor cell growth and invasion (Hood and Cheresh 2002; Kurozumi et al. 2012; Schnell et al. 2008). Cilengitide is a cyclic peptide containing an RGD sequence that binds and inhibits integrin activation and signaling (Scaringi et al. 2012). This drug is capable of antagonizing αvβ3 integrin at sub-nanomolar concentrations, and in case of α3β1 and α5β1 integrins at low nanomolar concentrations. Cilengitide also induces detachment and apoptosis in αvβ3 and αvβ5 integrin-expressing cells in culture (Taga et al. 2002). Using human xenograft models of GBM, Cilengitide suppressed tumor growth and showed anti-angiogenic and anti-tumorigenic properties (Buerkle et al. 2002; MacDonald et al. 2001; Mitjans et al. 2000; Onishi et al. 2013). These cellular outcomes are achieved through cytotoxic, anti-angiogenic, as well as anti-invasive effects (Kurozumi et al. 2012). Phase III trials in glioma are ongoing. (Eskens et al. 2003; Hariharan et al. 2007; O'Donnell et al. 2012). Early data suggest that overall survival remains modest, even though Cilengitide effectively accesses integrin targets in glioma cells and intratumoral blood vessels (Gilbert et al. 2012).

7.8.2 Sorafenib

Sorafenib is a small molecule inhibitor of VEGFRs, PDGFRs, and other kinases (Siegelin et al. 2010). In phase I clinical trials Sorafenib tested as a monotherapy or in combination with bevacizumab (Scott et al. 2010) or with radiation and temozolomide (Den et al. 2013) resulted in only modest increases in overall survival, although to date the phase II trial results have not been reported. In vitro studies have shown that sorafenib treatment of glioma cells caused a marked reduction in cell proliferation and increased apoptosis that correlated with reduced phospho-MEK and phospho-MAPK levels (Du et al. 2012). The protein kinase C δ inhibitor rottlerin has also been reported to potentiate antigrowth effects of sorafenib (Jane et al. 2006).

7.8.3 Marimastat

During blood vessel sprouting and remodeling various ECM proteins within the vascular basement membrane must be degraded. These are made possible by a class of proteins known as matrix metalloproteinases (MMPs). MMP2 (gelatinase A) and MMP9 (gelatinase B) are particularly important in glioma angiogenesis. These proteinases are secreted as proactive molecules and membrane-bound MMPs cleave and activate these proteins (Markovic et al. 2009). In comparison to normal brain and low-grade astrocytomas, GBMs overexpress many MMPs, likely leading to increased invasiveness. For example, MMP9 expression was detected at very low levels in normal brain and low-grade astrocytomas, but strong protein expression was reported in GBM (Hagemann et al. 2012). In addition, MMPs actively contribute to tumor angiogenesis by facilitating pericyte release from vascular basement membranes, releasing ECM-bound growth factors, and releasing pro-migratory ECM components helping in directed migration and in disruption of EC–cell adhesion (Rundhaug 2005). Marimastat is an MMP inhibitor that is orally administered. Activation of MMPs has proven to be essential for the tumor cell migration and angiogenesis. Various clinical trials have been conducted in different types of cancer. A phase I study identified the toxicity level of this drug with mild to severe muscle and joint pain. A phase III trial performed in different cancers, including glioma, showed only minimal improvements in overall survival (Levin et al. 2006; Steward and Thomas 2000).

7.8.4 Other Anti-vascular Agents

Thalidomide is an angiogenesis inhibitor, although the exact mechanism of action is not completely understood. Reduced expression of αvβ3 and αvβ5 integrins, as well as VEGF-A, has been reported as possible modes of action. However, clinical trials conducted using thalidomide as a monotherapy failed to improve prognosis (D'Amato et al. 1994; Fine et al. 2000; Onishi et al. 2011). Imatinib is a tyrosine kinase inhibitor of PDGFR, c-Kit, Bcr-Abl, and other targets. This compound has been shown to induce apoptosis at high concentrations. Monotherapy using imatinib was unsuccessful and did not result in clinical benefits (Morris and Abrey 2010; Radford 2002). Tenascin-C is a pro-migratory protein overexpressed in tumor ECs in GBM. Inhibition of tenascin-C using neutralizing antibodies might block angiogenesis and thereby glioma progression. However, phase II clinical trial conducted using administration of neutralizing antibodies failed to achieve survival benefits to GBM patients (Reardon et al. 2002; Zagzag et al. 1996, 2002).

7.9 Future Directions

Targeting angiogenesis was one of the more promising strategies for inhibiting tumor growth and progression, particularly in highly vascularized gliomas. Early preclinical and clinical studies yielded promising results; however, the efficacies of anti-angiogenic therapies remain in question as many reports indicate recurrence of tumors with infiltrative and drug-resistant growth properties, especially in GBM. Activation of alternative signaling pathways or compensation by pro-angiogenic molecules likely accounts for tumor recurrence and drug resistance. For example, inhibition of VEGF resulted in upregulation of placental growth factor and FGF. VEGF was also upregulated after VEGFR or EGFR inhibition, and IL8 was upregulated after HIF1α gene deletion (Carmeliet 2005). Additional mechanisms of resistance include "angiogenic mimicry" where tumor cells can transdifferentiate to ECs and contribute to blood vessel functions. Hence, once the ECs are functionally inactive, the tumor cells adapt into the function of ECs integrating into the vessel wall (El Hallani et al. 2010; Ricci-Vitiani et al. 2010; Soda et al. 2011a). This transdifferentiation is not limited to ECs, but tumor cells also give rise to mural cells such as pericytes (Cheng et al. 2013; Scully et al. 2012). Dedifferentiation of neurons and astrocytes can also contribute to gliomagenesis (Friedmann-Morvinski et al. 2012).

Another mechanism by which glioma cells acquire resistance to anti-angiogenic therapies is via enhanced invasion to distal brain regions. Mechanisms of tumor cell invasion after Bevacizumab treatment are now under intense investigation. For example, Lu et al. have shown that this invasion is mediated through c-Met activation (Lu et al. 2012) while research from our laboratory has revealed the importance of integrin αvβ8 in tumor cell invasion (Reyes et al. 2013; Tchaicha et al. 2011). A better understanding is needed for how blood vessels develop and remodel under normal and neoplastic conditions and how their regulation is altered after anti-angiogenic therapies. Combination therapies that target angiogenic effectors or both angiogenic and invasive components may lead to more effective therapies for treating gliomas.

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