Histol Histopathol (2016) 31: 1069-1078

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

The role of integrins in primary and secondary brain tumors

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Summary. The tumor environment plays an integral part in the biology of cancer, participating in tumor initiation, progression, and response to therapy. Integrins, a family of cell surface receptors, bridge the extracellular matrix to the intracellular cytoskeleton. Since their first characterization 25 years ago, a vast amount of work has been performed to understand the essential role of integrins in cell development, tissue organization, tumor growth, vessel development and their signaling mechanisms. Their potential as therapeutic targets in various types of cancer is intensively studied. In this review, we discuss the expression patterns and functional role of integrin in primary brain tumors and brain metastases, provide an overview of clinical data on integrin inhibition and their potential application in imaging and therapy of these tumors.

Key words: Integrin, Extracellular matrix, Immunohistochemistry

Introduction

Many brain tumors are associated with considerable morbidity and poor prognosis. They may originate from neuronal or glial elements within the brain, or they may represent the spread of distant cancers.

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DOI: 10.14670/HH-11-7741

Gliomas are the most frequently occurring primary intraaxial brain tumors. The most common glioma type is the glioblastoma WHO grade IV (GBM). The majority of these tumors appear "de novo" after a short clinical history. In contrast, approximately 10% of the tumors manifest in younger patients as secondary glioblastomas, progressing from diffuse astrocytoma (grade II and III) precursor (Ohgaki and Kleihues, 2013). Morphologically indistinguishable, GBM of different age groups and tumor location comprise several different biologic entities with defined driver mutations such as IDH, H3F3A and TERT (Appin et al., 2015). Macroscopic complete neurosurgical resection of these tumors is only possible in some patients because of the highly infiltrating growth pattern. In high-grade (ie. WHO grade III and IV) lesions, surgical resection is followed by postoperative therapeutic interventions, including radiation therapy and alkylating chemotherapy, yet the prognosis often remains poor (Stupp et al., 2009; Venur et al., 2015).

Metastatic brain tumors are more common than primary brain tumors. Approximately 20-40% of patients with malignant neoplasms will develop brain metastases (Mehta et al., 2005; Nayak et al., 2012). The incidence of single vs multiple sites of central nervous system (CNS) metastasis is similar (Tsao et al., 2012). A formidable complication of brain metastases is the spread of tumor cells along the cerebrospinal fluid (neoplastic meningitis) and is seen in up to 15% of the cases (Chamberlain, 2012). Common anatomic sites of primary tumors are breast, lung cancer and skin (melanomas). Together they account for up to 80% of all CNS metastases (Nayak et al., 2012). The prognosis of

brain metastases is usually very poor, with a median survival of 4-6 months even after whole brain radiotherapy (Sundstrom et al., 1998, Lagerwaard et al., 1999) although in some cases there is the possibility of long-term survival (Lutterbach et al., 2002). Prognostic factors include tumor location, number of metastases, response to steroid treatment (Lagerwaard et al., 1999) and in breast cancer a positive HER2 status with appropriate treatment (Bartsch et al., 2012).

Mechanism of tumor spread and the role of the extracellular matrix

Among glial brain tumors, diffuse gliomas (ie. astrocytoma, oligodendroglioma and glioblastoma) are characterized by extensive diffuse tumor cell spread in the CNS neuropil with only minimal destruction of the preexisting neuronal structures (Scherer 1940). The intrafascicular, perifascicular and interfibrillary growth is predominantly observed along blood vessels and prominently myelinated axons such as the corpus callosum (Giese and Westphal, 1996). Consequently, almost half of the tumours have spread to contralateral hemispheres at the time of diagnosis (Matsukado et al., 1961). Glial tumour spread involves several steps including local degradation, migration into the newly created space and re-adhesion to local matrix proteins. Laminin and collagen, the classical components of the extracellular matrix (ECM) and potent stimulators of glioma growth (Giese et al., 1995), are usually not observed directly adjacent to the glial tumor cells, except in desmoplastic transformed tumor areas (Paulus and Tonn, 1994). Instead, tenascin is upregulated at the invasive edge of gliomas, surrounding single invasive cells facilitating tumor migration (Zagzag et al., 1995). To breach the integrity of the ECM, glial tumor cells secrete matrix-degrading proteases, serine proteases and matrix metalloproteinases, all of them upregulated in tumours compared to normal brain (Nakagawa et al., 1994; Allmendinger et al., 2012). Cell adhesion is then mediated by ECM receptor families such as cadherins that include NCAM and CD44, selectins and the integrins (Denda and Reichardt, 2007). Because migration of tumor cells along basal membrane containing structures is most likely mediated by specialized receptors, the integrin receptor family has moved into the focus of researchers.

Brain metastasis includes several steps, including detachment of tumor cells from primary site, intravasation into vessels, extravasation, hiberniation in vascular niches, proliferation and invasion to their target (Winkler, 2015). In the last steps, the highly specialized tumor brain microenvironment plays an important role. Not only does the blood brain barrier (BBB) limit penetration of active substances or immunomodulatory cells, but also astrocytes, pericytes and microglia contribute directly to tumor cell colonization in the brain (Fidler 2011). Brain metastases usually show a surrounding gliosis by increased number of reactive astrocytes. It has been demonstrated that astrocytes protect tumor cells from chemotherapy-induced cytotoxicity (Lin et al., 2010). The tumor cells themselves gain access to the surrounding parenchyma and promote their growth through induction of angiogenesis (Langley and Fidler, 2011). The ECM involvement is crucial for this last challenging step and it is thought that less than 1% of the circulating tumor cells are successful in forming metastasis (Barkan et al., 2010; Langley and Fidler, 2011) A specific tumor-ECM interaction provides a good explanation for the predilection of specific tumor types in selected organs ("seed and soil" hypothesis by Stephen Paget (Paget, 1889)). Very recent data indicate that this organotropism is mediated by tumour exosomes containing specific integrin components (Hoshino et al., 2015).

The structure and role of integrins in the human brain

The ECM is essential for architectural support of tissue, regulation of cell proliferation and differentiation (De Archangelis and Georges-Labouesse, 2000). The composition of the ECM macromolecules is tissue-dependent and may vary within the tissue itself and in response to reactive stimuli (Jones and Jones 2000; Radisky et al., 2002). Epithelial (and in neoplasms, the carcinoma) cells are separated from the surrounding stroma by the basement membrane, a specialized ECM. Major constituents of the ECM are laminins, collagens, proteaoglycans, fibronectins and tenascins. Not surprisingly, these ECM macromolecules are often upregulated in glioma and brain metastases (Radisky et al., 2002).

Integrins consist of a superfamily of cell adhesion receptors that bind to extracellular matrix (ECM) proteins and cell-surface ligands. The name "integrin" was coined in 1986 for these integral membrane protein complexes after their first characterization (Tamkun et al., 1986). They are heterodimeric transmembrane receptors at the cell surface that have a key role in the crosstalk between the cell and its surrounding stroma (Takada et al., 2007). Integrins are obligate non-covalently interacting alpha / beta heterodimers; each chain has a large extracellular domain and, with the exception of $\alpha v\beta 4$, a short cytoplasmic domain. The size varies but typically the α- and β-subunits contain around 750 to 1000 amino acids. By combination of at least currently recognized 18 α-subunits and 8 β -subunits, twenty-four different integrin heterodimers are formed (Plow et al., 2000). The proteins are usually present in a "bent" conformation that would place the ligand binding site near the membrane surface. The ligand-binding properties of these heterodimers is determined by the alpha subunit; some of them have only a single beta-subunit partner (Cox and Huttenlocher, 2000). Among the alpha subunits αv is most remarkable for having

multiple beta partners that do not bind to other alpha subunits (αvβ3, αvβ5, αvβ6 and αvβ8). The non-enzymatic cytoplasmic tails and the transmembrane helices are essential for coordination of cellular response upon activation by binding of extracellular ligands (Cox et al., 2010). Alternatively to this outside-in signaling, integrins can be activated directly by intracellular proteins which results in modification of the extracellular parts (inside-out signaling) (Hynes 2002). This bidirectional integrin activity might explain their different functional, sometimes opposite, role in cell fate (Desgrosellier and Cheresh, 2010).

Usually, Integrins are not constitutively active (Tabatabai et al., 2011; Seguin et al., 2015). Ligand binding activates cytoplasmic kinase cascades which regulate cell attachment, tissue differentiation, cell migration and growth (Hynes, 2002). This activation includes several important intracellular pathways, including mitogen-activated protein kinase, serine/threonine kinase and tyrosine kinase (Clark and Brugge, 1995) pathways. The interaction of the αv-family (and α5β1, and αIIbβ3) of integrins is mediated by binding to specific arginine-glycine-aspartic acid (RGD) sequences of the ECM ligands (eg. vitronectin, fibronectin, osteopontin and fibrinogen), while α4β1, α4β7, and α9β1 bind to an acidic motif, termed "LDV," that is functionally related to RGD (Hynes, 2002; Campbell and Humphries, 2011). Some integrins, especially αvβ6 and αvβ8 have been associated with local activation of TGF-β (Sheppard, 2004) and this integrin-mediated activiation of TGF-β1 via the aryl-hydrocarbon receptor is necessary for proper function of this key controlling molecule (Platten et al., 2000; Siligner et al., 2015).

In the developing brain, integrins spatiotemporally contribute in a cell-specific manner for distinct patterns of neuronal migration, cortical layer formation and differentiation within the cortex through interaction with neurotrophic factors (Schmid and Anton, 2003). Neural crest cells, the precursor cells derived from the dorsal neural tube, express many integrins and especially β 1 seems to be essential for Schwann cell differentiation (Feltri et al., 2002). The αv integrin subunit is expressed in radial glia fibers of the developing cerebral cortex and remains persistent in mature astrocytes (Hirsch et al., 1994). Of the β integrins, β1, β5, β8 integrin are expressed in all regions of the developing cerebrum and their expression persists in the adult animal cortex, while β6 is restricted to neuronal cells and β2, β3, β4 are completely absent (Cousin et al., 1997; Nishimura et al., 1998). The adult human brain parenchyma is characterized by a αvβ3 negative / αvβ5 negative / αvβ6 negative / αvβ8 positive phenotype (Schittenhelm et al., 2013a). Loss of β1 results in abnormal lamination of the cortex and cerebellum (Gleeson and Walsh, 2000). In the cerebelleum, β1 enhances the proliferative potential of the external granule cell layer to sonic hedgehog signaling that is relevant for stimulating neuronal precursors (Blaess et al., 2004). Blockade of α3β1 in animal models results in retarded radial and tangential neuronal migration (Schmid and Anton, 2003). Integrins are expressed at most synapses in the brain, and genetic and pharmacological studies indicate that they are required for normal synaptic plasticity but are not involved in synapse formation (Denda and Reichardt, 2009). Although αvβ8 and β1 integrins are present in normal human oligodendrocytes, data from animal models lacking β8 or β1 indicate that they are not required for normal myelinisation (McCarthy et al., 2005).

However, parenchymal αvβ8 is required for normal vascular development in the brain. Absence of αvβ8 results in increased brain hemorrhages. Surprisingly, the brain endothelia do not express αvβ8 but are surrounded by αvβ8 positive perivascular astrocytes guiding the vessel outgrowth (Arnold et al., 2014). Normal human brain vessels also do not express αvβ3 and αvβ6 but are positive for αvβ5 (Schittenhelm et al., 2013a). The possible role of some integrins in neurodegenerative diseases has sparked some interest, because they are expressed in Alzheimer plaques (Eikelenboom et al., 1994). Microglial phagocytosis of fibrillar amyloid in Alzheimer disease seems to be mediated by a integrin β1 dependent mechanism (Koenigsknecht and Landreth, 2004). Data on this subject, however, remains quite limited.

Table. Integrin targeting strategies (selection).

Substance	Strategy type	Target	Status	References
Cilengitide	RGD-based antagonist	αvβ3/αvβ5	clinical	Carter, 2010, Stupp et al., 2010, Nabors et al., 2012
S137, S247	RGD-peptidomimetic	αvβ3/αvβ5	preclinical	Shannon et al., 2004
S36578-2	RGD-peptidomimetic	αvβ3/αvβ5	preclinical	Maubant et al., 2006
Etaracizumab (Abegrin)	antibody	αvβ3	clinical	Hersey et al., 2010
Intetumumab (CNTO95)	antibody	αvβ3, αvβ1, αvβ5, αvβ6	clinical	Heidenreich et al., 2013
ATN-161	antagonist	α5β1	clinical	Cianfrocca et al., 2006
DI17E6	Nanoparticle-coupled antagonist	αv	clinical	Uhl et al., 2014
Fluciclatide	Radiolabelled RGD peptide	αvβ3/αvβ5	clinical	Sharma et al., 2015
IRDye 800CW-RGD	Fluorescence labelled RGD peptide	αvβ3	preclinical	Huang et al., 2012
Abituzumab	antibody	αv	clinical	Élez et al., 2015
Volociximab	antibody	α5β1	clinical	Barkan and Chambers, 2011

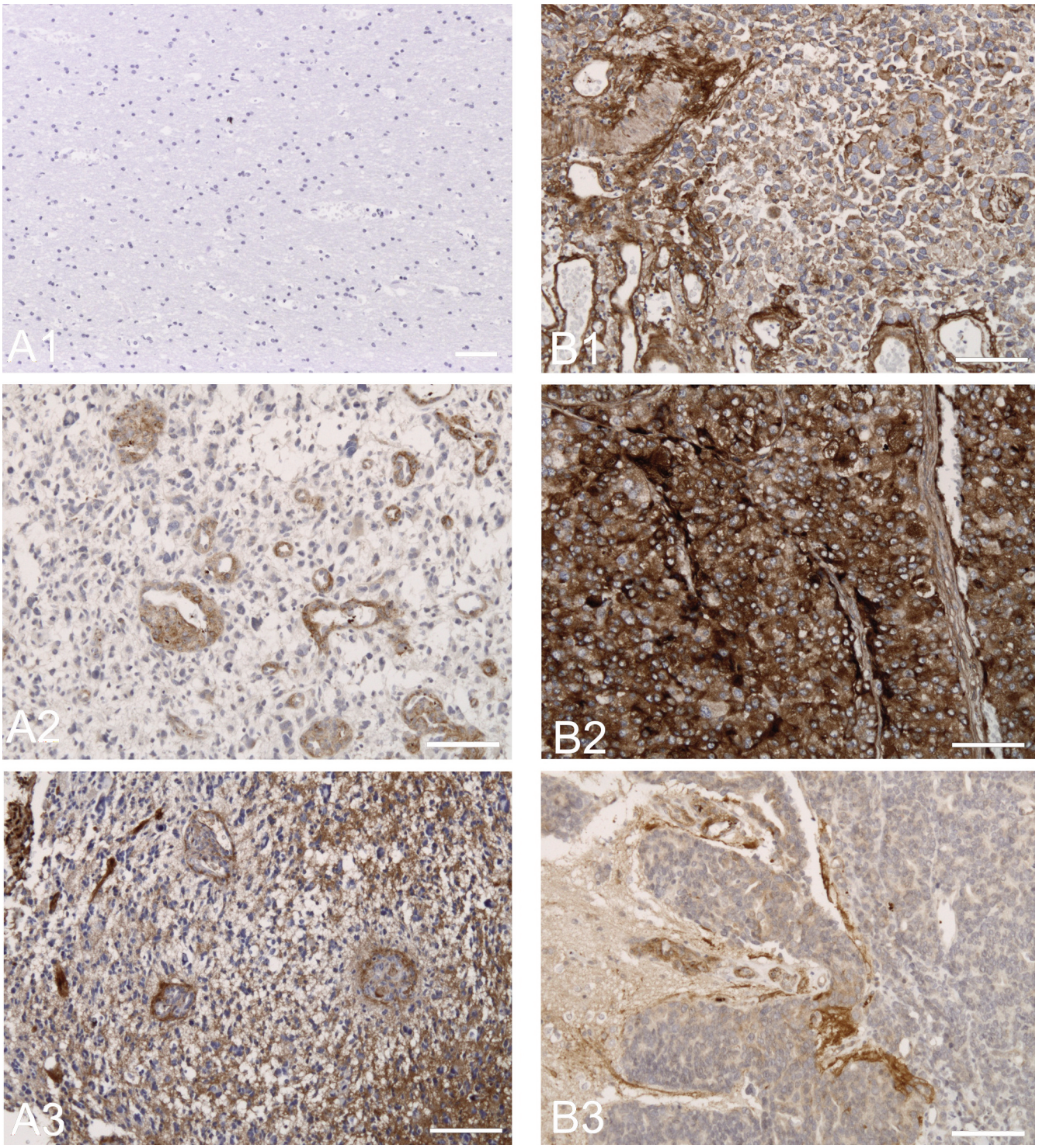

Fig 1. Example for the role of integrins in brain tumors (**A:** glioma, a primary brain tumor, **B:** Secondary brain tumor, metastatic adenocarcinoma). **A1.** In normal white matter human brain, αvβ3 expression is absent. **A2.** Upregulation of αvβ3 in primary glioblastoma vessels. **A3.** Glioma tumor infiltration border shows additional parenchymal upregulation of αvβ. **B1.** Carcinoma primary with partial αvβ5 expression in the tumor cells. **B2.** Strong upregulation of αvβ5 in brain metastasis. At the tumor-brain interface αvβ3 upregulation in the CNS indicates remodeling of the extracellular matrix along carcinoma tumor spread. Scale bars: 100 μm.

Role of integrins in glioma and brain metastasis biology

Like other constituents of the ECM, the integrins have a fundamental role in several types of cancer (Worthington et al., 2011). Alterations in integrin expression accompany and may contribute to the ability of cancer cells to cross physiological barriers in their tissue of origin and allow them to invade other structures (Caccavari et al., 2010). Recent data indicate that integrins are capable of regulating cancer stemness, and drug resistance (Seguin et al., 2015). The receptors for the extracellular signals providing increased proliferation of the cells are mainly β1 integrin-containing complexes (Park et al., 2000). Several important growth cascades are regulated through β1 including epidermal growth factor receptor (EGFR platelet-derived growth factor receptor (PDGFR) and the vascular endothelial growth factor receptor (VEGFR). The αv subunit is generally moderately to highly expressed in most brain tumors, while the corresponding β complexes are more dependent on the tumor type. Integrin αvβ6 is associated with cells of epithelial lineage and is rapidly upregulated on during tissue injury for activation of latent transforming growth factor β 1 (TGF-β1). In contrast, reactive astrocytes display a αvβ6 negative / αvβ8 positive phenotype (Schittenhelm et al., 2013a; Vogetseder et al., 2013).

In gliomas, especially α5β1, αvβ3 and αvβ5 integrins, which are frequently expressed in tumor endothelia and in some tumor cells, may affect glioma tumor initiation and progression (Aavramides et al., 2008). In contrast, αvβ3 is absent in non-neoplastic vessels (Gladson, 1996). Already the first studies in 1991 noted that αvβ3 expression in glioma cells is increased with tumour grade (Gladson and Cheresh, 1991). Subsequent larger immunhistochemical studies revealed that α3, αv, β1, β3 and β4 are regularly expressed in neoplastic astrocytes and are often upregulated compared to normal brain (Paulus et al., 1993). As expected from the αvβ3 expression, one major ligand of αvβ3, Osteopontin is similarly overexpressed in gliomas. In addition, detailed analysis revealed α6β4 upregulation in neoplastic astrocytes, while α6β1 remained unchanged compared to normal brain (Previtali et al., 1996). Integrin α5β1 expression correlates with a worse prognosis in high-grade glioma and α5β1 blockade triggered a caspase (Casp) 8/Casp 3-dependent strong apoptosis in glioma cells expressing a functional p53 (Renner et al., 2016). Because integrin β8 is expressed in most gliomas (~95%), regardless of WHO grading, a combination of of integrin complexes has diagnostic potential, especially an αvβ8-positive/ αvβ6-negative immunoprofile might help determine whether a tumor is of glial origin (Schittenhelm et al., 2013a). This is useful, when the glial fibrillary acidic protein immunophenotype in late-stage dedifferentiated GBM is equivocal. Surprisingly, data on integrin expression in other brain tumor entities such as oligodendroglial and ependymal tumors is very limited, but a single study indicates that expression is similar to astrocytic neoplasms (Paulus et al., 1993). Data from embryonal tumors is also very scarce, a few studies indicate that at least αv and α3 complexes are present in these tumors (Kishima et al., 1999; Thompson et al., 2013). Except for a single pilocytic astrocytoma immunreactive for β1 integrin, no studies in pediatric glial/glioneuronal tumors has been performed so far.

Direct inhibition of the αv complex resulted in migration arrest of glioma cells, suggesting that the αv-complex related integrins are more relevant in tumors than those associated with the β1 complex (Treasurywala et al., 1998). Subsequent functional studies with αvβ3 neutralizing antibody inhibited glioma cell migration in αvβ3 expressing cell lines (Wild-Bode et al., 2001). Integrin β3-knockout mice display enhanced tumor growth and a proangiogenic phenotype which has led to the concept that β3 expression may mediate a balance between protumor and antitumor effects (Hodivala-Dilke, 2008). This data indicates that αvβ3 integrin plays a key role in malignant gliomas and is a promising target for treatment. There is controversial data as to what extent αvβ3 blockading agents are effective, ie. stopping the migratory properties or even resulting in tumor cell death (Tabatabai et al., 2011). Recent obervations indicate that the tumor vascular pathology and hemorrhage seen in high-grade gliomas may be related to loss of parenchymal αvβ8 (McCarty et al., 2005).

In solid tumours the expression of integrin complexes is highly tissue dependent. For example, αvβ3 is prominently expressed in melanomas, αvβ5 in renal and colorectal carcinoma, αvβ6 is associated with lung adenocarcinomas, gastric cancer and pancreatic ductal adenocarcinomas (Mittelbronn et al., 2012; Schittenhelm et al., 2013b, Sipos et al., 2004) and αvβ8 is consistently expressed in gliomas and in some renal carcinomas. Prostate cancer is characterized by a α5β1+/ α7β1+/ αvβ5+ phenotype (Schittenhelm et al., 2013b; Drivaloset al., 2016). In breast cancer integrin complexes show a broad diversity. Approximatly 20% of the tumours are positive for at least one complex of α9β1 αvβ5, αvβ6 (Arihiro et al., 2000; Mittelbronn et al., 2012). Other publications report αvβ5 expression in up to 90% of breast cancer samples (Vogetseder et al., 2013). These discrepancies are most likely due to the poor ability of some integrin antibodies to stain formalin-fixated, paraffin-embedded (FFPE) samples. Recently developed recombinant rabbit monoclonal antibodies not only recognize integrins in FFPE material with high signal-to-noise contrast, but also bind intact extracellular domains of the targets, and show reproducibly results on automated immunohisto-chemistry systems (Goodman et al., 2012).

Brain metastases show divergent invasion patterns, designated well-demarcated, vascular co-option and diffuse infiltration (Berghoff et al., 2013). Levels of αvβ6 integrin were significantly higher in the well-

demarcated group than in the vascular co-option and the diffuse infiltration groups, indicating that αv integrin complexes influence the growth behaviour of solid cancers. Expression patterns of the αv integrin complexes differ between primary and metastatic lesions. For example in lung cancer brain metastases, vascular αvβ3 expression was more frequently than in primary lesions (Berghoff et al., 2014). In contrast, parenchymal expression of αvβ5 and αvβ6 were often higher in primary tumors compared to their brain deposits (Schittenhelm et al., 2013b). Melanomas showing parenchymal αvβ3 expression have a higher metastatic potential (Felding-Habermann et al., 2002). In many solid tumours α5β1 upregulation is associated with a poor prognosis (Schaffner et al., 2013).

Targeting the ubiquitous expressed αv integrin complex with intetumumab in a brain metastasis model resulted in reduced brain metastasis formation (Wu et al., 2012). In breast cancer cell lines, integrin β3 knockdown in combination with integrin antagonist treatment resulted in increased radiosensitization in a previously non-responsive cell line (Lautenschlaeger et al., 2013). Silencing of integrin β1 in breast-cancer cell lines resulted in decreased migration and invasion in cell lines. Furthermore an increased integrin β1 gene level (ITGB1) was associated to lower survival in patients with triple-negative breast cancer (Klahan et al., 2016). Reduction of integrin β4 and β6 in triple-negative breast cancer cell lines through penfluridol inhibited growth in introduced metastatic brain tumors (Ranjan et al., 2016).

Integrins as therapeutic target in brain tumors

Because of the functional role of αv integrins in brain tumors several integrin inhibitors have been developed. For a detailed overview the reader is referred to the review by Tabatabai et al. (2011). Drugs targeting specific arginine-glycine-aspartic acid (RGD) sequences of integrins that are present in the "on-state" of the receptors are extensively tested to deliver anticancer molecules or contrast agents for improved diagnosis. The affinity of RGD peptides for their ligands is highly dependent on peptide conformation and flanking amino acid sequences that influence receptor selectivity (Liu et al., 2015). Cilengitide is the most widely studied RGD αvβ3 and αvβ5 antagonist and has undergone phase III clinical trials (Carter, 2010). By modification of the guanidine groups it is possible to obtain a αvβ6-specific ligand or αvβ6/α5β1-biselective affinity (Kapp et al., 2016). Preclinical and initial phase II studies demonstrated a significant tumor growth inhibitory effect of cilengitide in glioblastoma (Stupp et al., 2010; Nabors et al., 2012). Yet, phase III studies with cilengitide in patients with lung cancer or metastatic melanoma or recurrent or metastatic head and neck tumours showed little effect on overall survival. Furthermore, Cilengitide given in combination with the standard drug temozolomide in glioblastoma patients did not improve overall survival (Stupp et al., 2014). This might be due to the limited pharmacokinetic properties of cilengitide with biweekly infusions of 2000 mg. In addition these studies might further highlight the necessity for patient selection in future trials with integrin inhibition strategies, e.g. by RDG PET.

Other integrin-targeting approaches include RGD-grafted nanoparticles or liposomes that are internalized by integrin-mediated endocytosis and then localized in perinuclear regions (reviewed by Danhier et al., 2012). RGD-targeted nanocarries require ligand-binding for uptake, otherwise the coupled drugs are gradually released by the cell. Preclinical studies included RGD carriers coupled with paclitaxel, doxorubicin and gemcitabine in carcinoma and glioma cell lines. It is thought that αvβ3-positive vasculature is destroyed due to local cytotoxic effects thus resulting in oxygen deprivement of the nearby tumor cells. These RGD strategies are also exploited to deliver radionucleotides or serve as a radiotracer such as [18F]-Galacto-RGD in PET and SPECT (Haubner et al., 2014). Another RGD radiolabeled marker with high affinity for αvβ3/αvβ5 integrin, Fluciclatide is currently being tested to assess angiogenesis in solid tumors (Sharma et al., 2015). Intraoperative tumor visualization through near-infrared fluorescent imaging of integrin expression in glioblastoma models has recently sparked some interest. The RGD-coupled probe called IRDye 800CW-RGD was capable of binding specifically to integrin β3 and showed a high tumor to normal brain fluorescence ratio in glioblastomas (Huang et al., 2012).

Alternative approaches include monoclonal antibodies and non-RGD antibodies. Etaracizumab is a humanized monoclonal antibody that showed promising results in experimental studies but failed to show a benefit in phase 2 studies (Hersey et al., 2010). Apparently this substance is no longer tested in clinical trials (Tabatabai et al., 2011). Abituzumab targeting integrin αv heterodimers has demonstrated preclinical activity and has been tested in metastatic colorectal cancer indicating that a subgroup may benefit from this therapy (Élez et al., 2015). Inhibitors targeting the α5β1 component such as ATN-161 and Volociximab in dormant metastatic tumor cells have been recently tested in phase 1 studies (Barkan et al., 2011). Vedolizumab binds to the α4β7 integrin complex and is used for the treatment of ulcerative colitis but has currently no role in cancer tretament. S247, an RGD peptidomimetic αvβ3 antagonist in combination with fractionated radiotherapy demonstrated reduced cell proliferation and increased radiosensivity though inhibition of the Akt phosphorylation in human glioma xenograft models (Abdollahi et al., 2005). Another RGD-mimetic, S 36578 showed antiangiogenic properties in endothelial cells but is currently no longer evaluated (Maubant et al., 2006; Tabatabai et al., 2011).

Conclusions

Among the extracellular matrix proteins, the

integrins are a critical component in determining the growth and metastasis of tumors. Specific integrin complexes are one of the major mediators for the brain organotropism by tumour exosomes in carcinoma and melanoma metastasis. In primary brain tumors, integrins contribute to the ability of glioma cells to migrate and invade preexisting brain parenchymal structures. The upregulation of divergent integrin complexes in most cancers associated with malignancy and metastatic behavior may serve as a diagnostic as well as prognostic biomarker. While direct antagonism treatment failed in larger studies, the coupling of molecules with high affinity to selective integrins via the RGD-motif provides not only new therapeutic approaches but also has potential for specific preoperative tumor imaging. Subsequent studies are needed to explore whether exosomal anti-integrin strategies can be used in cancer therapeutics.

Acknowledgements. JS is funded by the Else-Übelmesser foundation of cancer research, Baden-Württemberg, Germany (Grant 30.19845). The funders had no role in the decision to publish, or preparation of the manuscript.

Footnotes Conflict of interest. GT served on advisory boards for MSD, Roche Switzerland, BMS, received travel grants from MSD, Medac, Roche Switzerland and received research grants from Roche Diagnostics. BS received research grant from Merck, Novartis, travel grant from Roche and is member of NET Advisory board of Novartis. The authors declare that they have no competing interests.

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Accepted April 14, 2016