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Angiogenesis of Primary Brain Tumors: The Role of Endoglin (CD105)

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1. Introduction

Angiogenesis is the process by which tumors induce the blood supply crucial for growth and progression. Therefore, angiogenesis has been proposed as a prognostic marker in a variety of human neoplasms (Bellamy et al., 1999). Although the importance of angiogenesis in solid tumors is well established, its role in the clinical implication of neoangiogenesis in brain tumors is enigmatic.

Endoglin (CD105) is a receptor for transforming growth factors (TGF)- β 1 and TGF-beta 3, and it modulates TGF- β signaling by interacting with the TGF- β a receptor I (TGF- β RI) and/or the TGF- β receptor II (TGF- β RII) whereas antibodies against panendothelial cells, such as anti-CD31 and anti-CD34 antibodies, have been commonly used in the evaluation of angiogenesis. These panendothelial antibodies react with not only newly forming vessels, but also with normal vessels trapped within tumor tissues (Duff et al., 2003). On the other hand, endoglin (CD105) is predominantly expressed in cellular lineages within the vascular system and is overexpressed in proliferating endothelial cells that participate in tumor angiogenesis, with weak or negative expression in the vascular endothelium of normal tissues (Balza et al., 2001). Investigators have recently shown that endoglin (CD105) is a more specific and sensitive microvessel marker than other commonly used panendothelial antibodies in malignant neoplasms of the brain, breast, colon, esophagus, urothelial bladder, and lung (Dales et al., 2004; Bodey et al., 1998; Minhajat et al., 2006; Saad et al., 2005; Santos et al., 2003; Tanaka F et al., 2010).

From this perspective, this review summarizes our current knowledge regarding the role of endoglin (CD105) in the angiogenesis of primary brain tumors and further introduces the potential role of endoglin (CD105) targeting compounds for the treatment of primary brain tumors.

2. Structure and function of endoglin (CD105)

Endoglin was designated the cluster of differentiation number 105 at the Fifth International Workshop on Human Leukocyte Differentiation Antigen. Therefore, it was called, as an alias, CD105 (Dallas et al., 2008). Human endoglin (CD105) is a type I integral membrane protein with a large extracellular domain, a single hydrophobic transmembrane domain, and a short cytosolic domain. The expression of two alternatively spliced isoforms (L and S), long and short endoglin has been characterized. L- endoglin and

S-endoglin are different from each other in their cytoplasmic tails that have 47, 14 amino acids, respectively. L- endoglin is predominant and S-endoglin remains unobscure in the significance of its function (López-Novoa & Bernabeu, 2010). Endoglin is constitutively phosphorylated on serine and threonine residues. Endoglin is an accessory protein of the TGF- β receptor family (Barbara et al., 1999; Li et al., 1999). The TGF- β receptor family of ligands contains TGF- β type 1, TGF- β type 2, and TGF- β type 3 isoforms and activins, and bone morphogenic proteins. The cytosolic domain of endoglin serves as a receptor transforming factor (TGF)- β type 1 and TGF- β type 3, and modulate TGF- β signaling through its interaction with TGF- β RI and TGF- β RII. In endothelial cells, two TGF- β receptor type 1 pathways with opposite effects have been demonstrated: the ALK-5 that stimulates Smad 2/3 phosphorylation, and the ALK-1 that stimulates Smad 1/5 phosphorylation. Endoglin (CD105) induces TGF- β 1/ALK 5 signaling that promotes endothelial proliferation and migration. On the other hand, endoglin (CD105) indirectly inhibits TGF- β 1/ALK 5 signaling (Dallas et al., 2008;Fonsatti et al., 2010).

3. Endoglin (CD105) and hypoxia

Hypoxia is a major stimulus of neovascularization including tumor angiogenesis, and collateral vessel formation in ischemic cardiovascular disease. As outlined above, endoglin (CD105), a marker of endothelial cells, is abundantly expressed in tissues undergoing angiogenesis and is a receptor for transforming growth factor β . The pivotal role of CD105 in the vascular system was demonstrated by the severe vascular defects that occur in CD105-knockout mice, but the exact mechanisms for CD105 regulation of vascular development have not been fully elucidated. In light of the function of CD105 and the importance of hypoxia in neovascularisation, Li et al. speculated that CD105 is involved in hypoxia-initiated angiogenesis, and they have investigated the effects of hypoxic stress on CD105 gene expression using tissue-cultured human microvascular endothelial cells (Li et al., 2003). As for the results, they considered that hypoxia is a potent stimulus for CD105 gene expression in vascular endothelial cells, which in turn attenuates cell apoptosis and thus contributes to angiogenesis. They also speculated that the non-TGF β -binding endoglin (CD105) in endothelial cells plays a self-protective role against apoptotic factors such as hypoxia.

Angiogenesis occurs in the human brain after a stroke, with endothelial proliferation after 3 to 4 days, a dense capillary network by 1 week, and neovascular infiltration by 2 to 4 weeks. These alternations help to sustain cerebral circulation and prevent a recurrent stroke. Therefore, to investigate the mechanisms of angiogenesis after cerebral ischemia, Zhu et al. studied the effect of hypoxia on endoglin expression in murine cerebral microvascular endothelial cells (bEND.3 cells) in vitro and the possible involvement of mitogen-activated protein kinase (MAPK) pathways (Zhu et al., 2003). The results of their investigation are as follows; namely, hypoxia increased endoglin mRNA and protein expression in bEND.3 cells, which was associated with the phosphoactivation of extracellular signal-related kinase (ERK), p38 MAPK, and Jun amino-terminal kinase (JNK). Inhibitors of p38 decreased the hypoxic induction of endoglin expression, as did dominant negative MAPK kinase 3 (MKK3), which activates p38. In contrast, constitutively active MKK3 or JNK1 potentiated the hypoxic induction of endoglin. Therefore, they considered that hypoxia induces the expression of endoglin at both the mRNA and protein levels and that induction is regulated by the p38 and perhaps also JNK pathways. In addition, Guo et al supported their theory

based on the data of human strokes, although it would limit the value of the findings of Zhu et al., which were based on the use of murine endothelial cell culture and an *in vivo* mouse model of focal cerebral ischemia (Guo et al., 2004). Furthermore, they demonstrated that knowledge of endoglin (CD105) signaling would have practical implications for the discovery of novel therapies in a host of angiogenic disease.

Dziewulska et al. morphologically examined human brains several years after a territorial ischemic stroke to assess the development of progressing white matter damage and its pathomechanisms (Dziewulska et al., 2006). They focused on the role of TGF- β , one of the factors whose expression increases after tissue damage, and its receptor endoglin in the propagation of postischemic injury. The results of their investigation are as follows; namely, the examination of white matter adjacent to the postapoplectic cavity revealed structural changes in the capillary vessels, disturbed microcirculation, and deep endothelial cell damage with DNA fragmentation in the TUNEL reaction. Many oligodendrocytes also revealed DNA damage and an increased expression of caspase-3. In the rarefied white matter, the microvessel immune reaction to TGF- β was diminished while the expression of endoglin was heterogeneous: absent in some capillaries but increased in others in comparison to the vessels located more peripherally from the cavity and in the control material. Therefore, they considered that endoglin and TGF- β can be involved in the development of the microangiopathy responsible for the propagation of postischemic white matter injury in humans, and speculated that disturbances in endoglin expression can influence TGF- β signaling and, consequently, vessel structure and function. In addition, they considered that pronounced endoglin expression can lead to decreased vessel wall integrity while a lack of the constitutively expressed protein is probably a reflection of deep vessel damage.

Collectively, these above studies indicate that endoglin (CD105) has an important role in angiogenesis in ischemic cardiovascular disease or cerebral stroke.

4. Endoglin (CD105) and non-tumor angiogenesis

Although endoglin is expressed at low levels in normal tissue, it is highly expressed in vascular endothelial cells during embryogenesis, in inflamed tissues, and healing wounds, psoriatic skin, inflamed synovial arthritis, and vascular injury. In addition, investigators pointed out the important role of endoglin in vascular pathology. Particularly, the representative example is hereditary hemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber syndrome (Fernández-L et al., 2006). This is manifested as epistaxis, mucocutaneous and gastrointestinal telangiectases, and arteriovenous malformations in the pulmonary, cerebral, or hepatic circulation. The recent isolation and characterization of circulating endothelial cells from HHT patients has revealed a decreased endoglin expression, impaired ALK1- and ALK5-dependent TGF- β signaling, disorganized cytoskeleton and the failure to form cord-like structures which may lead to the fragility of small vessels with the bleeding characteristic of HHT vascular dysplasia, or to disrupted and abnormal angiogenesis after injuries and may explain the clinical symptoms associated with this disease. Furthermore, it is well known that a high incidence of arteriovenous malformations (AVMs) of central nervous system is associated with HHT type 1 and endoglin. The gene mutated in this disorder is expressed at reduced levels in the blood vessels of these patients. Since endoglin is a component of the transforming growth factor- β receptor complex critical for vascular

development and homeostasis, Matsubara et al. determined its expression in sporadic cerebral AVMs and in normal brain vessels (Matsubara et al., 2011). They examined twenty cerebral AVMs and 10 normal brain samples were analyzed for endoglin, platelet endothelial cell adhesion molecule 1 (PECAM-1), alpha-smooth muscle cell actin, vimentin, and desmin by immunohistochemistry. As for the results of their investigation, in the normal brain, endoglin was found not only in the endothelium of all vessels but also in the adventitial layer of arteries and arterioles. Namely, in cerebral AVMs, the numerous vessels presented expressed endoglin in both the endothelium and adventitia. Arterialized veins, identified by lack of elastin and an uneven thickness of smooth muscle cells, revealed endoglin-positive mesenchymal cells in the adventitia and perivascular connective tissue. They found that these cells were fibroblasts since they expressed vimentin but not actin and/or desmin, and that increasing numbers of endoglin-positive endothelial and adventitial cells were seen in sporadic cerebral AVMs, but endoglin density was normal. Thus, they considered that it was not involved in the generation of these lesions. However, since the presence of endoglin in fibroblasts in the perivascular stroma, they speculated that there is an active role for this protein in vascular remodeling in response to increased blood flow and shear stress.

On the other hand, Sure et al. examined endoglin (CD105) expression of adult cavernous malformation of the central nervous system (CNS) to clarify their biological activity (Sure et al., 2005). They pointed out the histological similarities of HHT and the cavernous malformation of the CNS, and found endoglin (CD105) in the majority of cavernous malformations of the CNS. However, they considered that the role of endoglin (CD105) in cavernous malformations when compared with AVMs, since cavernous malformations are not associated with high blood flow or shear stress.

Moyamoya disease is a cerebrovascular occlusive disease characterized by progressive stenosis or occlusion at the distal ends of the bilateral internal arteries. Histological investigations on autopsy samples have demonstrated the main vascular lesion in moyamoya disease is stenosis or occlusion caused by an intimal hyperplasia. Recently, evidence has been obtained indicating that hypoxia-inducing factor-1 regulates TGF- β 3.

Therefore, Takagi et al. surgically collected tiny pieces of the wall of the middle cerebral artery from patients with moyamoya disease and analyzed them using histological and immunohistochemical methods focusing on the mechanism of remodeling of the intracranial arterial walls of patients with moyamoya disease (Takagi et al., 2007). As for results of their study, middle cerebral artery specimens from moyamoya disease patients had a thicker intima than those from the control group. In moyamoya disease samples, the immunoreactivity indicating both hypoxia-inducing factor-1 α and endoglin expression was higher in the endothelium and intima. No vascular endothelial growth factor immunoreactivity was detectable in the moyamoya disease samples. In addition, transforming growth factor- β 3 immunoreactivity was also detected and was co-localized with that of hypoxia-inducing factor-1 α and endoglin, mainly in the endothelium.

Therefore, they considered that hypoxia-inducing factor-1 α and endoglin were overexpressed in the intima of the middle cerebral artery of moyamoya disease patients, and that these factors play a role in the proliferating response of moyamoya disease.

Collectively, these above studies indicate that endoglin (CD105) has an important role in the vascular remodeling of the CNS.

5. Endoglin (CD105) and tumor angiogenesis

Angiogenesis is the formation of new blood vessels from preexisting vessels or circulating endothelial progenitor cells, and it is essential for tumor growth by providing nutrients and eliminating metabolic waste products. Therefore, angiogenesis has been proposed to be a prognostic marker in a variety of human neoplasms and investigators compared the expression of endoglin with other markers in cancers from various organs.

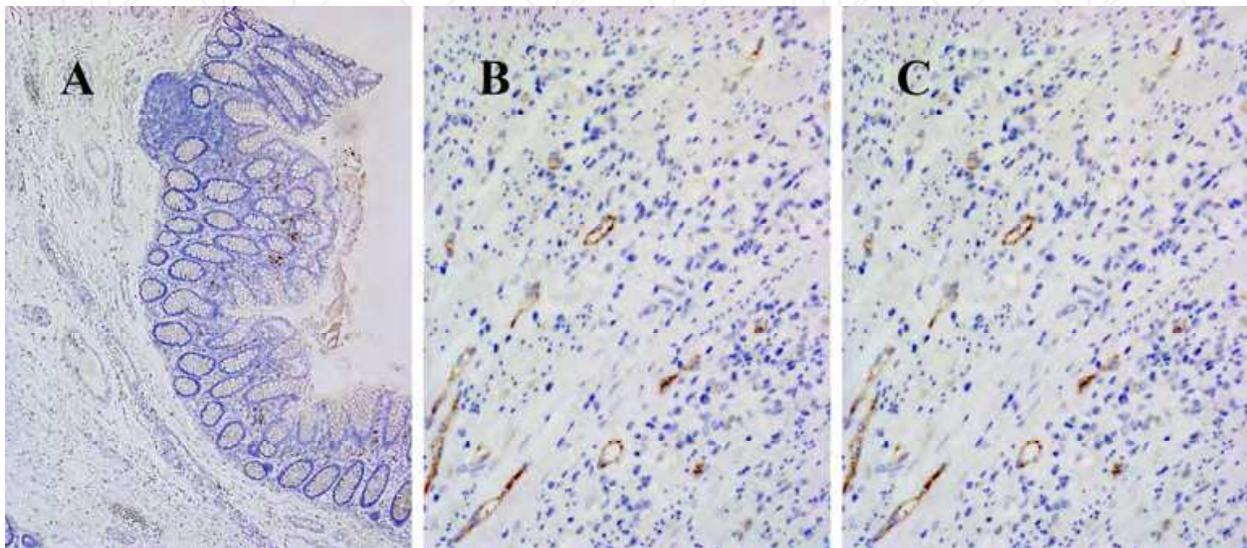
It was reported by Saad et al. that they studied endoglin and the vascular endothelial growth factor (VEGF) expression as a possible prognostic marker in esophageal carcinoma (Saad et al., 2005). They have shown that the assessment of microvessel count using endoglin in esophageal carcinoma might be a valuable parameter for predicting patients who have a poor survival rate and higher risk of developing a metastatic disease. In addition, they reported that endoglin, by direct staining of proliferative vessels in esophageal adenocarcinoma, is a more specific and sensitive marker for tumor angiogenesis than the other commonly used panendothelial markers. Furthermore, endoglin staining also showed prognostic significance with a positive correlation with the presence of angiolymphatic invasion, tumor stage, and survival.

In breast carcinomas, as in many tumor types, marked characteristics of neoangiogenesis have been found to correlate with a high rate of metastasis. Intratumoral tumoral microvessels can be identified with panendothelial markers that stain all tumor blood vessels to the same degree. Dales et al. therefore considered that they should examine other markers more specific to activated endothelial cells that should better reflect a tumor's capability to produce new vessels, and they studied the long-term prognostic significance of neoangiogenesis in breast carcinoma by comparison of Tie-2/Tek, endoglin (CD105) and CD31 immunocytochemical expression (Dales et al., 2004). As a result, they showed that endoglin (CD105) immunorexpression in breast carcinomas is an independent prognostic indicator in node-negative patients, better in terms of overall survival than Tie-2/Tek and panendothelial marker CD31.

Information regarding the role of angiogenin and endoglin (CD105) expression in head and neck squamous cell carcinoma is extremely sparse and limited exclusively to serum protein levels. Thus, Marioni et al. investigated angiogenin expression in laryngeal squamous cell carcinoma and evaluated the relationship between angiogenin expression and endoglin (CD105), clinicopathological and prognostic parameters. As a result, they showed that angiogenin expression in laryngeal carcinoma cells and endoglin (CD105) expression in vascular endothelial cells in the de novo blood vessels can be considered potentially useful to detect laryngeal squamous cell carcinoma patients with high risk of disease recurrence who might benefit from more aggressive therapy (Marioni et al., 2004).

Most colorectal carcinomas are considered to originate from precursor lesions (adenomas). Adenomas are thought to progress to carcinoma over many years because of multiple accumulated molecular alternations, and angiogenesis is an important step in the process of colorectal carcinoma growth. Therefore, Minhajat et al. compared the expression of endoglin (CD105) in several hundred target spots with that of other endothelial markers in all tissue layers during the development of colon carcinoma using tissue microarrays and immunohistochemistry (Minhajat et al., 2006a, 2006b). As a result, they showed that endoglin (CD105) was expressed at high levels in vascular endothelial cells in the de novo blood vessels of the adenoma-carcinoma of the colon and was weakly expressed in blood vessels of the normal mucosal layers. Therefore, they considered that endoglin (CD105) was

more intensely expressed in de novo microvessels. In this review, Fig. 1 shows that endoglin (CD105) was expressed at high levels in vascular endothelial cells in the de novo blood vessels of the carcinoma of the colon. Namely, although vascular endothelial expression of panendothelial marker CD 34 in normal and neoplastic layers of adenoma and adenocarcinoma from all layers did not significantly differ, endoglin (CD105) was intensely expressed in vascular endothelial cells of the neoplastic mucosal adenoma and various layers of adenocarcinoma at a level corresponding to the depth of cancer invasion.



A. Endoglin (CD105)-negative endothelial cells in normal colonic tissue adjacent to colonic carcinoma. B. Vessels in colonic carcinoma at submucosal level showing endoglin (CD105)-positive endothelial cells. C. Vessels in colonic carcinoma at muscular layer level showing endoglin (CD105)-positive endothelial cells.

Fig. 1. Expression of endoglin (CD105).

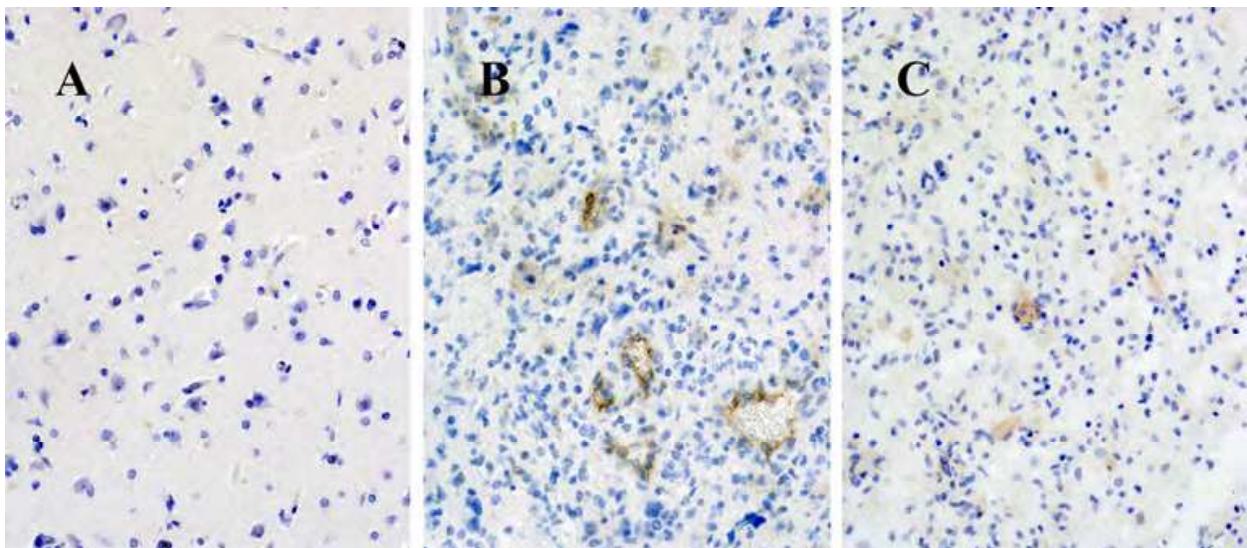
Collectively, these above studies indicate that endoglin (CD105) is a better marker than panendothelial markers such as CD31, 34, etc., in the evaluation of neoangiogenesis and prediction of prognosis in various cancers.

6. Endoglin (CD105) and primary brain tumor angiogenesis

6.1 Endoglin (CD105) and glioma angiogenesis

Several investigators have shown that the degree of angiogenesis has a prognostic value in glial tumors, particularly astrocytic tumors, oligodendrogliomas. Yao et al. considered that the prognosis of glioma patients is largely determined by the histopathological malignancy grade, whereas within each grade, the clinical course of glioma patients is still variable because each grade tumor is not a single pathological entity but encompasses a spectrum of tumors with variable malignant potential. Also, the prediction of tumor biological behavior can thus hardly be made only by histological criteria and needs the predicting assistance of biological makers (Yao et al., 2005). Therefore, they assessed microvessel density (MVD) using an anti-105 monoclonal antibody to clarify the validity of endoglin (CD105) in the evaluation of angiogenesis in gliomas. They demonstrated that MVD expressed by endoglin (CD105) is more closely correlated the prognosis of glioma patients than MVD expressed by panendothelial marker CD 31.

The prototypic histopathology of glioblastomas is characterized by dense cellularity, striking pleomorphism, a complex form of microvascular proliferation and zones of coagulative necrosis lined by “pseudopalisading” tumor cells. It is also well known that numerous vascular changes occur at the transition of anaplastic astrocytomas to glioblastomas. Recent studies have further demonstrated that a dramatic shift in biological behavior occurs following the transition from anaplastic astrocytomas to glioblastomas. Brat and Van Meir reported that pseudopalisade formation results from the following sequence of events: i) vascular occlusion, which is related to endothelial apoptosis and associated with intravascular thrombosis; ii) hypoxia in regions surrounding vascular pathology; iii) outward migration of glioma cells away from hypoxia, creating a peripherally directed wave of cell movement; iv) death of nonmigrated cells leading to central necrosis; v) an exuberant angiogenic response creating microvascular proliferation in regions peripheral to the central hypoxia; and vi) enhanced outward expansion of infiltrating tumor cells toward a new vasculature (Brat & Van Meir, 2004). In addition, vascular glomeruli are observed in the white matter surrounding the tumor but less frequently in the cortex. The number, caliber and wall thickness mean values of the vessels are significantly higher than those of the normal brain. In this area, significant modifications in terms of vascularization and biomolecular features take place. Therefore, Sica et al. investigated that neovascularization in the tumor surrounding areas by examining endoglin (CD105) and nestin expression along with MVD while establishing their possible prognostic significance (Sica et al., 2011). As a result, they demonstrated that a tumor neoangiogenesis occurs in glioblastoma peritumor tissue with intimate involvement of pericytes, and that endoglin (CD105)-MVD in the area located at a greater distance from the tumor margin carries prognostic significance. In this review, Fig. 2 shows that endoglin (CD105) is expressed at high levels in vascular endothelial cells in the de novo blood vessels of glioblastoma. Namely, although vascular endothelial expression of panendothelial marker CD 34 in normal and did not significantly differ normal brain, astrocytoma, and glioblastoma, endoglin (CD105) was intensely expressed in



A. Endoglin (CD105)-negative endothelial cells in normal brain tissue adjacent to glioblastoma. B. Vessels in Glioblastoma (Grade IV, WHO classification) showing intensive endoglin (CD105)-expression of endothelial cells. C. Vessels in diffuse astrocytoma (Grade II, WHO classification) showing heterogenous endoglin (CD105)-expression of endothelial cells.

Fig. 2. Expression of endoglin (CD105).

vascular endothelial cells of glioblastoma, but was heterogeneous in astrocytoma and negative in normal brain, respectively.

Regarding oligodendrogliomas, Netto et al. considered that oligodendrogliomas show typical vascularization with delicate and ramified blood vessels, but also the importance of angiogenesis (Netto et al., 2008). Therefore, they assessed microvessel density (MVD) using an anti-105 monoclonal antibody to clarify the validity of endoglin (CD105) in the evaluation of angiogenesis in oligodendrogliomas, and showed that endoglin (CD105)-MVD is greater in anaplastic oligodendrogliomas than oligodendrogliomas, indicating an increase in the vascular neof ormation, something which must be evaluated as a possible prognostic factor in oligodendrogliomas.

Based on these collective evidences, it is indicated that endoglin (CD105) is a better marker than panendothelial markers such as CD31, 34, etc., in the evaluation of neoangiogenesis and prediction of prognosis in glial tumors, particularly glioblastomas.

6.2 Endoglin (CD105) and extraaxial tumor angiogenesis

The grading of meningiomas is generally based on tumor subtype and histological features. Although the MIB-1 labelling index is not an included criterion in the WHO grading system, it is sometimes used to assess the prognosis of patients with meningiomas. In addition, several studies have shown that the morbidity of meningiomas is related to the degree of tumor vascularity. As mentioned above, several investigators have already shown that the degree of angiogenesis has prognostic value in primary brain tumors, particularly astrocytic tumors, oligodendrogliomas. Regarding extraaxial tumor angiogenesis, Barresi et al. investigated endoglin (CD105) in immunorexpression in meningiomas and the corresponding normal leptomeninges in order to evaluate its ability to identify newly formed neoplastic vessels as well as establish whether a correlation exists between clinicopathological parameters, so as to verify if MVD documented by endoglin (CD105) could be utilized for prognostic purposes (Barresi et al., 2008). As a result, they showed that CD 34 stained both the host entrapped vessels in meningiomas and the newly formed vessels; thus CD34 may be considered a pan-endothelial marker, while endoglin (CD105) further appears to be a more specific marker for neo-angiogenesis, and that endoglin (CD105) positive vessels were evidenced in 70% of meningiomas and atypical meningiomas were characterized by higher endoglin (CD105) immunorexpression in general. Interestingly, they also showed that cases with higher MIB-1 labelling indexed exhibit significantly higher CD 105 counts. In this regard, they speculated that meningiomas with an intrinsically higher capability to proliferate undergo a hypoxic condition which is determined by their increased volume, and that hypoxia may be in turn responsible for the endoglin up-regulation, via the hypoxia inducible factor-1 and consequently for the higher neo-angiogenesis revealed by MVD. Furthermore, they speculated that endoglin (CD105) might be considered a target for anti-angiogenic selective immuno-therapies able to blood supply in meningiomas.

Regarding pituitary tumors, there is controversy about the behavior of angiogenesis as a function of hormonal secretion or other characteristics of pituitary tumors. Pizarro et al. studied the anti-endoglin (CD105) antibody, a glycoprotein expressed in endothelial cells and conjunctive tissue particularly associated with neovascularization, in order to determine MVD in pituitary adenomas (Pizarro et al., 2009). Their data were as follows; No significant difference was found in MVD concerning the variables of age, clinical presentation, immunohistochemical phenotype or tumor size. MVD in males was significantly higher than in females. Cell proliferation, as evaluated by the MIB-1 antibody ranged from 0% to

19.58%. No correlation was found between MIB-1 and MVD. Therefore, they speculated that the lower MVD found in pituitary adenomas in females reflects an inhibitory estrogen action on TGF- β 1, a protein involved in vascular remodeling, and that, because of its role as a TGF receptor ligand, endoglin proved to be sensitive in detecting this gender difference in pituitary tumor angiogenesis.

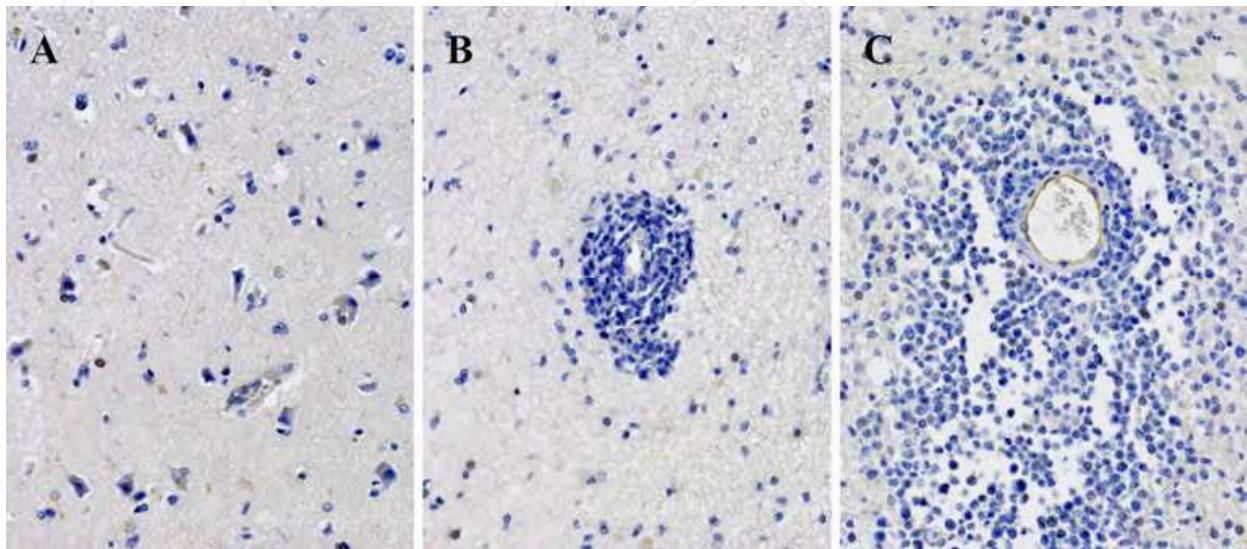
6.3 Endoglin (CD105) and primary central nervous system lymphoma angiogenesis

Primary central nervous system lymphomas (PCNSLs) are an uncommon variant of extranodal non-Hodgkin lymphomas that involve leptomeninges, eyes or the spinal cord without evidence of systemic disease. These lymphomas do not include systemic lymphomas that have spread to the CNS. The vast majority of PCNS lymphomas are of B-cell origin (Paulus et al., 2007; Sugita et al., 2004). There have been two hypotheses to explain the pathologic processes of PCNS lymphomas. One hypothesis suggests that inflammatory lesions transform into neoplasms, such as lymphomas, in situ in the CNS. The other hypothesis suggests that a malignant B-cell clone homes to the CNS, although a putative homing signal has not been identified.

There are conflicting descriptions as to whether the degree of angiogenesis as measured by microvessel density has prognostic value in lymphomas. For example, Zhao et al. reported that vascular endothelial growth factor-A was expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphomas, and it thus was related to lymphoma progression (Zhao et al., 2004). Salven et al. also demonstrated the simultaneous serum elevation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) levels to be an independent predictor of a poor prognosis in non-Hodgkin's lymphoma (Salven et al., 2000). On the other hand, Stewart et al. reported that non-Hodgkin's lymphoma may be less angiogenic than most solid tumors (Salven et al., 2002). Regarding PCNSLs, Rubenstein et al. speculated that angiotropism in PCNSLs may constitute an important paracrine growth mechanism for lymphoma progression (Rubenstein et al., 2002). However, Roser et al. commented that the lack of a correlation between apoptosis and vascularity may indicate that PCNSLs growth occurs independently of vessel formation, even though the high microvessel density in PCNSLs could play a significant role in the growth kinetics and infiltrating potential of the tumor. They also commented that this could be due to the various techniques for microvessel counting used by different laboratories rather than due to truly different results (Roser et al., 2004).

It was described by Sugita et al that CD105 staining reduced the false-positive staining of blood vessels in comparison to the commonly used panendothelial marker CD34. In addition, the survival rate of the lower-MVD patients was significantly higher than that of the higher-MVD patients when CD105 was used as a marker of angiogenesis. In contrast, when CD34 was used as a marker of angiogenesis, the survival rates did not significantly differ between these two groups. In addition, using a multivariate analysis, CD105-MVD demonstrated independent prognostic impacts in this investigation. As a result, they considered that the growth of PCNSLs was dependent on angiogenesis and that the intratumoral-MVD determined by the anti-CD105 monoclonal antibody was a reliable prognostic marker in patients with PCNSLs (Sugita et al., 2007). In general, PCNSLs are typically patchy, poorly demarcated, and angiocentric at low magnification (Russel & Rubinstein, 1989). Namely, the neoplastic transformation itself may, especially at the periphery of the tumor, remain at first relatively confined to the Virchow-Robin spaces, but thereafter may acquire a more florid

expression as it infiltrates and destroys the neural parenchyma. In view of their study on the angiogenesis of PCNSLs, there may be some validity to this theory. Therefore, they demonstrated that PCNSLs may not need sufficient neoangiogenesis at the start of PCNSLs, but instead may require a higher rate of neoangiogenesis as they infiltrate and destroy the brain parenchyma at an advanced stage. In this review, Fig. 3 shows that endoglin (CD105) is expressed at high levels in vascular endothelial cells in the de novo blood vessels of PCNSL.



A. Endoglin (CD105)-negative endothelial cells in normal brain tissue adjacent to PCNSL. B. Endoglin (CD105)-negative endothelial cells in the periphery of PCNSL. C. Vessels in an advanced stage of PCNSL showing intensive endoglin (CD105)-expression of endothelial cells.

Fig. 3. Expression of endoglin (CD105).

7. Endoglin (CD 105) antagonists: a potential therapeutic tool for malignant brain tumors

As outlined above, endoglin (CD105) has an important role in the tumorigenesis of malignant tumors. In addition, vascular targeting agents for the treatment of cancer are designated to cause a rapid and selective shutdown of blood vessels of tumors (Thorpe F et al., 2004). Thus, endoglin (CD105) is emerging as a prime vascular target of antiangiogenic cancer therapy. Interestingly, Takase et al. assessed cases of small cell carcinomas at autopsy using immunohistochemistry to investigate the degree of angiogenesis status in small cell carcinoma tissue (Takase et al., 2010). As a result, they considered that small cell carcinomas are predominantly supported by newly formed vessels that are generated by endoglin (CD105)-mediated angiogenesis, and that anti-angiogenic therapy, especially endoglin (CD105)-targeting, proved an effective form of small cell carcinoma treatment.

Recent studies have shown the systemic administration of naked antihuman endoglin monoclonal antibodies to suppress established tumors, and its efficacy was markedly enhanced by combination with a chemotherapeutic drug using an antiangiogenic schedule of drug dosing. For instance, the effect of anti-endoglin (CD105) monoclonal antibodies has been investigated in several animal models. Takahashi et al. showed that antiangiogenic therapy of established tumors in human skin/severe combined immunodeficiency mouse chimeras bearing human breast cancer by anti-endoglin (CD105) monoclonal antibodies,

SN6f, SN6j, SN6k (Takahashi et al., 2001). Namely, SN6j and SN6k were effective in suppressing established tumors, whereas tumor suppression was weaker with SN6f. A combination of SN6j and SN6k that defined mutually nonoverlapping epitopes showed an additive antitumor effect. A combination of SN6j and cyclophosphamide using an antiangiogenic schedule of drug dosing showed synergistic antitumor efficacy. They therefore considered that systemic administration of naked antihuman endoglin monoclonal antibodies can suppress established tumors, and the efficacy is markedly enhanced by combining a chemotherapeutic drug using an antiangiogenic schedule of drug dosing.

Anti-metastatic effects of an antitumor drug are extremely important. Thus, Uneda et al. investigated the anti-metastatic activity of 3 anti-endoglin monoclonal antibodies (SN6a, SN6j, SN6k) in animal models. They showed that SN6a and SN6j effectively suppressed the formation of metastatic colonies of murine mammary carcinoma cells in the lung of metastatic models and that SN6j, SN6k and their immunoconjugates with deglycosylated ricin A-chain were effective in suppressing hepatic metastasis of murine colorectal carcinoma cells (Uneda et al., 2009). As a result, they considered that data of their investigation were clinically relevant in view of a clinical trial.

Interestingly, it was shown by Lee et al that anti-angiogenic/anti-tumor effects achieved in a prophylactic setting with an oral DNA vaccine encoding murine endoglin, carried by double attenuated *Salmonella typhimurium* to secondary lymphoid organ, i.e., Peyer's patches (Lee et al., 2006). Their approach was as follows; After vaccination, mice were injected with D2F2 mouse mammary carcinomas and tumor progression was evaluated. As a result, unvaccinated mice had significantly more lung metastasis, but tumors in vaccinated mice were less angiogenic. In addition, the vaccinated mice had a longer overall survival. Regarding the effects of an oral DNA vaccine, they speculated that a CD8⁺ T cell mediated immune response induced by this vaccine effectively suppressed dissemination of pulmonary metastasis of D2F2 breast carcinoma cells presumably by eliminating proliferating endothelial cells in the tumor vasculature. They therefore considered that the vaccine strategies can contribute to future therapies for breast carcinomas.

Regarding brain tumors, Bodey et al. investigated 62 childhood brain tumors including 34 medulloblastomas and 28 astrocytomas for the assessment of endoglin (CD105) expression (Bodey et al., 1998). Their assessment was as follows: Strong expression of endoglin (CD105) on endothelial cells was demonstrated in all 62 childhood brain tumor cases. The most striking feature of the newly formed tumor-related capillaries was the presence of a markedly enlarged perivascular space. Blood vessels in several normal human tissues (cortex, cerebellum, thymus, tonsil, spleen, lymph node, skin) used as control tissues contained significantly lower levels of endoglin (CD105), in accordance with the extremely slow turnover rate of normal endothelial cells. A close apposition between the capillaries and the adjacent parenchyma was also observed. VEGF/PF-R1 (flt-1) and VEGF/PF-R2 (flk-1) are formed *de novo* in a glioma progression-dependent manner. Therefore, they considered that brain tumors, especially glioblastomas, are among the most vascularized human neoplasms, and thus are candidates for antiangiogenic therapy. In addition, they further demonstrated points that substantiate the importance of endoglin (CD105) in the earliest possible detection, diagnosis and neoplasm-related angiogenesis inhibition-based treatment of mammalian solid neoplasms, especially in childhood brain tumors.

At present, a phase 1, first-in human study with the human/murine chimeric anti endoglin (CD105) monoclonal antibody TRC105 is ongoing in patients with refractory advanced or metastatic solid carcinomas (Fonsatti et al., 2010, Seon et al., 2011).

8. Conclusion

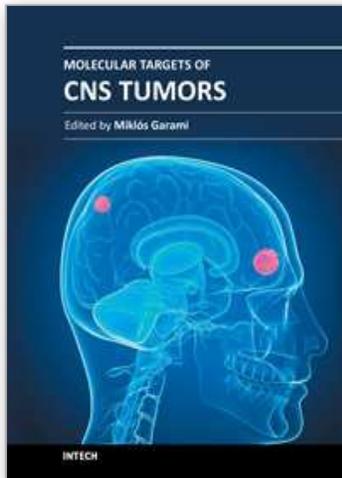
As outlined above, endoglin (CD105) has an important role in tumorigenesis of malignant tumors. In addition, based on these collective evidences, it is indicated that endoglin (CD105) is a better marker than panendothelial markers, such as CD31, 34, etc., in the evaluation of neoangiogenesis and prediction of prognosis in primary brain tumors, particularly glioblastomas. Furthermore, endoglin (CD105) is emerging as a prime vascular target of antiangiogenetic cancer therapy. Recent studies have shown the systemic administration of naked antihuman endoglin monoclonal antibodies to suppress established tumors, and that its efficacy is markedly enhanced by combination with a chemotherapeutic drug using an antiangiogenic schedule of drug dosing. Therefore, the results of endoglin expression in gliomas, PCNLs, and other primary brain tumors could thus eventually lead to better performance of therapeutic trials on antiangiogenic treatment for patients with these primary brain tumors.

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