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Review

The hypoxic peri-arteriolar glioma stem cell niche, an integrated concept of five types of niches in human glioblastoma

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ABSTRACT

Glioblastoma is the most lethal primary brain tumor and poor survival of glioblastoma patients is attributed to the presence of glioma stem cells (GSCs). These therapy-resistant, quiescent and pluripotent cells reside in GSC niches, which are specific microenvironments that protect GSCs against radiotherapy and chemotherapy. We previously showed the existence of hypoxic peri-arteriolar GSC niches in glioblastoma tumor samples. However, other studies have described peri-vascular niches, peri-hypoxic niches, peri-immune niches and extracellular matrix niches of GSCs. The aim of this review was to critically evaluate the literature on these five different types of GSC niches. In the present review, we describe that the five niche types are not distinct from one another, but should be considered to be parts of one integral GSC niche model, the hypoxic peri-arteriolar GSC niche. Moreover, hypoxic peri-arteriolar GSC niches are structural and functional look-alikes of hematopoietic stem cell (HSC) niches in the bone marrow. GSCs are maintained in peri-arteriolar niches by the same receptor-ligand interactions as HSCs in bone marrow. Our concept should be rigidly tested in the near future and applied to develop therapies to expel and keep GSCs out of their protective niches to render them more vulnerable to standard therapies.

1. Introduction

Glioblastoma is the most common, aggressive and lethal primary brain tumor with poor patient survival of approximately 15 months post-diagnosis despite extensive treatment including surgery, irradiation and chemotherapy. This low survival rate is at least partly caused by glioma stem cells (GSCs) [1,2]. Until now, we and others have used the term *glioma stem-like cells* for GSCs because of the lack of specific markers to unequivocally detect GSCs [3–9]. Because the current evidence of the contribution of GSCs to glioma progression is extensive [10–15], we propose to use the term *GSCs* from now on. The distinct self-replicating pluripotent GSCs reside in niches, which are specific microenvironments in glioblastoma where GSCs are maintained. GSCs are resistant to therapy and may cause tumor recurrence [16–19]. Therapy resistance is induced by quiescence of GSCs in their niches [20–27], a strong and efficient DNA damage response after therapy [19,20,26,28], high drug efflux ABC transporter activity [20] and/or Notch signaling [19,25]. However, interactions between GSCs and their niches are not well understood and this poor understanding prevents the development of effective therapeutic strategies to eradicate GSCs [17–19,29]. Hyperthermia in combination with irradiation is a promising therapeutic approach to target therapy-resistant GSCs, since multiple DNA repair pathways are sensitive to hyperthermia [30]. Our ultimate aim is to force GSCs out of their protective niches to be able to target them more efficiently with standard cytotoxic therapies.

So far, peri-vascular niches [29], peri-arteriolar niches [7,9,31],

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CatK, cathepsin K; CXCR4, C-X-C receptor type 4; DLL4, Delta-like ligand 4; GSC, glioma stem cell; EC, endothelial cell; ECM, extracellular matrix; GM-CSF, granulocyte/macrophage colony-stimulated factor; HIF, hypoxia-inducible factor; HSC, hematopoietic stem cell; HSP, hypoxia stress-induced chaperone protein; J1, Jagged-1; M-CSF, monocyte chemoattraction protein-1; MMP, matrix metalloprotease; MSC, mesenchymal stem cell; NO, nitric oxide; OPN, osteopontin; SDF-1α, stromal-derived factor-1α; SHH, Sonic Hedgehog; SCF, stem cell factor; TAM, tumor-associated macrophage; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1

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Table 1
Characteristics of the five types of GSC niches.

Niche type	Histological characteristics	Cells or macromolecular components	Functional proteins/markers
Peri-vascular	Irregular vascular membranes, vascularization	ECs, pericytes	SDF-1α, CXCR4, SHH, DLL4, J1, CD31, CD34, CD36, type 1 collagen, laminin-8, tenascin-C, fibronectin, MMP, HIF-1α, VEGF
Peri-arteriolar	Arterioles in hypoxic areas	ECs, pericytes, smooth muscle cells	CD31, SMA, SDF-1α, CXCR4, OPN, CatK, CD44, HIF-1α, VEGF
Peri-hypoxic	Necrosis	ECs	HIF-1α, HIF-2α, VEGF, SDF-1α, CXCR4
Peri-immune	Necrosis	Macrophages, bone marrow-derived monocytes	MCP-1, periostin, OPN, neurotensin, SDF-1α, CXCR4, VEGF
ECM	Around arteriolar adventitia, hypoxic/necrotic areas	Proteoglycans, extracellular vesicles, fibroblasts, stromal cells	Type 1 collagen, laminin-8, tenascin-C, fibronectin, MMP, HIF-1α, VEGF

peri-hypoxic niches [32], peri-immune niches [33] and extracellular matrix (ECM) niches [34] have been described for GSCs. Each type of niche contains specific cell types and proteins that are responsible for specific molecular mechanisms and unique interactions with GSCs. In the peri-vascular niche, GSCs are located in close association with endothelial cells (ECs) that line blood vessels [3,23,35]. In the peri-arteriolar niche, proteins such as stromal derived factor-1α (SDF-1α) and its receptor C-X-C receptor type 4 (CXCR4) have been found to be located around ECs [7,9,31]. In peri-hypoxic niches, transcription factors such as hypoxia-induced factors (HIFs) are important in the regulation of stemness [18,32,35] but expression of HIFs is also important in peri-vascular niches and peri-arteriolar niches. In peri-immune niches, GSCs have been shown to induce differentiation of bone marrow-derived monocytes and microglial cells into tumor-associated macrophages (TAMs) [36,37]. In ECM niches, markers have been identified that play a crucial role in the process of angiogenesis [34,38–40].

Each type of niche harbors types of cells, proteins and/or molecular mechanisms that are in some cases unique to that specific type of niche and are in some cases shared between various types of niches. Therefore, this review critically evaluates all known cell types, proteins and molecular mechanisms that have been associated with each of the five types of GSC niches that have been described so far, and we describe a novel concept of 1 integrated niche model, the hypoxic peri-arteriolar GSC niche. GSC niches are most likely present in the angiogenic and hypoxic center of glioblastoma tumors whereas the outer parts are invasive [41,42,125].

2. Description of the five types of GSC niches

The cell types that have been associated with one or more of the five GSC niches are listed in Table 1, and proteins associated with the GSC niches are listed in Table 2.

2.1. Peri-vascular niches

The most frequently-described GCS niche type is the peri-vascular GSC niche in which endothelial cells (ECs) are crucial to control GSC stemness [16–19,29]. ECs are derived from hematopoietic stem cells in the bone marrow [43] and markers such as CD31 [7,44], CD36 [45] and CD34 [29] are used to detect and visualize ECs immunohistochemically. GSCs express VEGF that promotes angiogenesis, one of the most important hallmarks of glioblastoma [29,35]. There is *in vivo* evidence that co-cultures of ECs and GSCs promote expression of stemness proteins, such as SOX2, OLIG2, BMIL and CD133 in GSCs [46] and that stemness of GSCs is maintained [19,29]. *In vitro* experiments showed that basic fibroblast growth factor (bFGF)-conditioned medium of glioblastoma-derived ECs induce dedifferentiation of glioblastoma cells into GSCs [11]. CD133-positive GSCs are localized in close vicinity of ECs [29,47] and *in vivo* ablation of blood vessels decreased the number of glioblastoma cells in glioblastoma xenograft models [29]. Nitric oxide (NO) is released by ECs that induces Notch signaling in nestin-positive GSCs that express the NO receptor soluble guanylyl cyclase. The Notch signaling pathway is essential for GSC maintenance [3,48,49].

Pericytes and smooth muscle cells are also functional cell types in the peri-vascular GSC niche [16,17,50]. Pericytes are involved in glioblastoma progression by promoting angiogenesis [17,50]. It has been reported that GSCs can transdifferentiate into ECs and pericytes which means that GSCs have the capability to differentiate into other cell types, in all probability to generate the cell types required to construct their niches [22,50,51]. *In vivo* cell lineage tracing data showed that the majority of pericytes in glioblastoma tumors are generated from GSCs and elimination of GSC-derived pericytes disrupted angiogenesis [50]. These findings imply that targeting pericytes, as part of the peri-vascular GSC niche, may be an effective therapeutic strategy for glioblastoma.

Table 2
Cell biological functions of GSC niche-associated proteins.

GSC niche-associated proteins	Function	References
SHH	- Activates SHH pathway - Increases expression of stemness genes (CD133, OCT4, OLIG2, NANOG, SOX2) - Supports glioblastoma cell proliferation and self-renewal	[46,64]
DLL4	- Activates Notch pathway by binding to Notch receptor on GSCs - Promotes glioblastoma tumor proliferation - Expressed by ECs	[19,28,35,65]
J1	- Activates Notch pathway - Promotes glioblastoma tumor proliferation - Expressed by ECs	[28,35,65]
VEGF	- Promotes angiogenesis - Induces DLL4 expression on ECs - Expressed by GSCs and TAMs - Expressed in hypoxic conditions	[17,29,35,49,66]
CD31, CD36, CD34	- EC markers - Involved in leukocyte transmigration, integrin activation and angiogenesis	[3,7,44,108]
CD44	- Promotes HSC/GSC phenotype and homing in niches - Increases radioresistance	[7,79,126]
SDF-1α	- Chemoattractant for CXCR4-positive cells - Involved in the migration and maintenance of HSCs - Produced by ECs, osteoblasts and GSCs - Involved in the recruitment and or development of TAMs - Expressed in hypoxic areas - Enhances angiogenesis	[7,15,19,62,76,79,81,95,97]
CXCR4	- Receptor for SDF-1α - Interaction with SDF-1α enables homing of stem cells in niches	[7,15,62,76,79]
OPN	- Chemoattractant for CD44-positive cells - Promotes stemness in GSCs - Enhances the function of HIF-2α	[7,79,96,126]
CatK	- Cysteine cathepsin that cleaves SDF-1α in bone marrow - Overexpressed in glioblastoma	[7,62,63,83]
SMA	- Marker for smooth muscle cells of arterioles	[9,78]
HIF-2α	- Transcription factor that upregulates stemness genes SOX2, OCT4 and CD133 - Expressed in hypoxic microenvironments - Specifically expressed by GSCs - Promotes self-renewal, proliferation and survival of GSCs *in vitro*	[19,32]
HIF-1α	- Transcription factor expressed in hypoxic microenvironments - Involved in GSC survival - Stimulates expression of SDF-1α, OPN and CD44 - Induces angiogenesis	[18,19,32,76]
MCP-1	- Chemoattractant - Promotes recruitment of TAMs to glioblastomas to enhance glioma tumor proliferation	[3,17,102]
GM-CSF	- Contributes to survival of bone marrow-derived monocytes	[33]
Periostin	- Extracellular matrix protein - Recruits TAMs and enhances glioma tumor proliferation - Involved in the binding of integrins on cancer cells leading to increased cell survival and angiogenesis	[56,99,100,103,104]
Neurotensin	- Chemoattractant for GSCs and TAMs	[4,65]
Type 1 collagen	- Most abundant collagen in non-cancerous ECM - Secreted by GSCs	[47]
Laminin-8	- ECM component - Largest constituent of blood vessel lamina basalis - Secreted by ECs	[39,40,75]
Tenascin-C	- ECM component - Activates Notch signaling to promote proliferation of GSCs	[71,73]
Fibronectin	- ECM component - Increases glioma cell survival	[72,77]
MMP	- Degrades ECM - Increases glioblastoma invasion	[57,58,61,80]

The structure of blood vessels in peri-vascular niches in glioblastoma is different from that of the vasculature of healthy brain tissue [52]. Blood vessels in glioblastoma are dilated and often leaky [16,29,52], which results in an altered blood flow, poor oxygen supply and subsequently a hypoxic microenvironment of GSCs [53,54]. Hypoxia as a distinct feature of the GSC niche is discussed in detail in Section 2.4.

Fibroblasts are also present in peri-vascular niches. Fibroblasts are responsible for ECM synthesis but also for ECM breakdown. For the latter purpose, fibroblasts express matrix metalloproteases (MMPs), which are proteases that degrade the ECM [55–58]. Degradation of the ECM is required for invasion [57,59–61] and extracellular expression of MMPs as well as cysteine cathepsins are associated with increased invasiveness of glioblastoma cells [3,34,62,63].

VEGF is expressed by, among other cell types, GSCs and ECs. Furthermore, ECs in the peri-vascular niche express Sonic Hedgehog (SHH) [46,64], Delta-like ligand 4 (DLL4) [35,65] and Jagged-1 (J1) [35]. SHH is involved in activation of the Hedgehog signaling pathway, which controls proliferation of normal stem cells in various organs and also GSCs [46,64]. SHH is involved in glioblastoma tumor growth, whereas knock down of DLL4 and J1 in ECs reduced glioblastoma growth *in vivo* [46]. Both ligands activate the Notch signaling pathway, which is an essential stem cell pathway [65,66]. GSCs express Notch receptors for these ligands and therefore have active Notch signaling pathways [64,65]. Table 2 gives a detailed outline of the cell biological functions of these proteins and other GSC niche-associated markers.

2.2. Extracellular matrix niches

The ECM is usually considered as part of peri-vascular niches and peri-arteriolar GSC niches [19,46,67]. In a small number of publications, the ECM is considered to be a distinct niche [16,34,38]. Especially, ECs in the peri-vascular niche secrete components of the ECM, such as (glyco)proteins, proteoglycans and extracellular vesicles [16,68–70]. The effects of interactions between GSCs and specific ECM components on GSC stemness need to be unraveled, particularly because GSCs are able to actively remodel their niches by deposition of their own ECM components, such as type 1 collagen [34,47] and fibronectin [16,71,72]. In this way, GSCs create their own niches [47].

Other ECM proteins in peri-vascular niches include laminins and tenascin-C [68,73,74]. These ECM proteins affect angiogenesis in peri-vascular GSC niches, but are not necessarily expressed by GSCs [75]. Tenascin-C, for instance, is expressed by differentiated glioblastoma cells [60,76] whereas tenascin-C has also been described as potential marker of GSCs [74,77]. The effect of tenascin-C on proliferation *in vitro* has been studied using blocking antibodies against tenascin-C which resulted in reduced proliferation of glioblastoma cells [60]. Furthermore, laminin is expressed in peri-vascular niches by ECs and is associated with glioblastoma tumor progression [16,40]. Ljubimova et al. [40] reported that expression of a specific type of laminin, laminin-8, is associated with glioblastoma recurrence. Besides, immunohistochemistry and western blot analysis showed that overexpression of laminin-8 is associated with a significantly shorter period of time to glioblastoma recurrence [40].

Taken together, GSCs directly and indirectly synthetize their own ECM by, for example, induction of tenascin-C expression by differentiated glioblastoma cells and laminin expression by GSC-associated ECs [16,34,47].

2.3. Peri-arteriolar niches

In 2015, Hira et al. were the first to demonstrate peri-arteriolar niches of GSCs by performing immunohistochemistry on cryostat sections of human glioblastoma [7]. CD133-positive and nestin-positive GSCs were shown to reside in hypoxic environments surrounding CD31-positive ECs and SMA-positive smooth muscle cells of arterioles [7]. Peri-arteriolar hypoxia was explained by the fact that arterioles are transport vessels and not exchange vessels whereas capillaries are the exchange vessels. The niches were always found in close vicinity of necrotic areas and expression of HIF-1α and VEGF was found around the arterioles in wider areas than the GSC niches [7]. Later on, Hira et al. repeated their investigations in a semi-quantitative manner in a larger number of human glioblastoma samples and found niches around 7 of 335 arterioles and none around 924 venules and 8085 capillaries [9]. The study characterized various proteins in peri-arteriolar GSC niches that appeared to be a replica of hematopoietic stem cell (HSC) niches in human bone marrow [7,9,31,79]. These proteins include stromal-derived factor-1α (SDF-1α), it receptor C-X-C receptor type 4 (CXCR4), cathepsin K (CatK), CD44 and osteopontin (OPN) [7,9,62,79].

SDF-1α and CXCR4 are involved in migration of HSCs and their homing in HSC niches [79–81]. SDF-1α and CXCR4 are predominantly expressed in hypoxic conditions in human bone marrow [80]. The receptor CXCR4 binds to the chemoattractant SDF-1α in HSC niches in bone marrow around arterioles [7,79,82]. SDF-1α and OPN are produced by ECs and osteoblasts [80]. The function of SDF-1α and OPN is to maintain HSCs in their niches *via* interactions with their receptors CXCR4 and CD44, respectively [79]. CatK is among the highest differentially-expressed proteases in glioblastoma as compared to the healthy brain [63,83]. Functionally, CatK can cleave and thereby inactivate SDF-1α in bone marrow, which leads to the release of HSCs out of HSC niches into the blood circulation [7,81,84]. An *in vitro* study demonstrated how inactivation of SDF-1α inhibits the binding of CXCR4-positive GSCs to SDF-1α [62]. It was suggested that in glioblastoma, SDF-1α and OPN are associated with homing of GSCs in niches *via* interactions with the GSC receptors CXCR4 and CD44, respectively, and that CatK plays a significant role in migration of GSCs out of niches [62].

2.4. Peri-hypoxic niches

Li et al. were in 2009 the first to report the effects of hypoxia and low oxygen levels in GSCs [32]. Exposure to a hypoxic environment induced expression of SOX2, OCT4 and CD133 in glioblastoma cells, which are GSC markers and indicate dedifferentiation of glioblastoma cells into GSCs [32,85]. It was concluded that a hypoxic microenvironment increased the expression of stem cell markers [16,17,86] and of HIFs [3,16,17,65,86]. Functionally, expression of HIFs results in production of pro-angiogenic growth factors and therefore induces angiogenesis [12]. HIF-1α and in particular HIF-2α are functional proteins of the family of HIFs, which individually contribute to the stemness of CD133-positive and CXCR4-positive GSCs in niches that express SDF-1α [10,18,19,32,41,87]. Immunohistochemical staining of HIF-1α and HIF-2α on glioblastoma biopsies showed their expression in these peri-hypoxic niches [19,32]. HIF-2α in contrast to HIF-1α directly promotes the GSC phenotype by upregulating the expression of SOX2, OCT4 and CD133, whereas HIF-1α was observed to play a more general role in GSC survival [87]. Moreover, HIF-1α is a less specific functional component of the peri-hypoxic niche of GSCs since HIF-1α is also expressed in other non-cancerous cells, whereas HIF-2α is specifically expressed by GSCs [19,32,87].

Hypoxia causes acidification of the microenvironment, which upregulates expression of HIFs and thus GSC maintenance [12]. Acidosis is, among others, induced by aerobic glycolytic production of lactate, elevated activity of carbonic anhydrase and ion transporters [12,88] and may be important for the activity of cysteine cathepsins, such as CatK and CatL [89–93]. Acidosis is an important factor for GSCs in peri-necrotic niches and this implies that pharmacological or genetic inactivation of HSP90, a hypoxia stress-induced chaperone protein expressed in the acidic microenvironment, inhibits expression of HIFs and reduces the tumorigenic and self-renewal characteristics of GSCs [12,22,87].

2.5. Peri-immune niches

Recently, a fifth niche has been described, in which specific immune cells, CD11b-positive tumor- associated macrophages (TAMs), play a major role [94]. TAMs are either pro-inflammatory and thus anti-cancer (M1-type TAMs) or anti-inflammatory and thus pro-cancer (M2-type TAMs) [17,19,33,94–96]. M2-type TAMs are essential for tumor progression in several types of cancer, including glioblastoma. TAMs are either differentiated bone marrow-derived monocytes [37] or originate from locally active macrophages (microglial cells) in the brain [17,37,97]. GSCs are able to differentiate into M2-type TAMs [3]. TAMs can also differentiate into ECs which suggests that ECs are components of peri-immune niches [17]. In peri-hypoxic niches, pro-inflammatory factors such as RAGE, COX2 and NF-kB are overexpressed, which suggests interactions between TAMs and GSCs [98]. GSCs express growth factors and chemoattractant proteins such as neurotensin, SDF-1α, VEGF, granulocyte/macrophage colony-stimulating factor (GM-CSF), macrophage CSF (M-CSF), monocyte chemoattraction protein-1 (MCP-1), MCP-3 and periostin that recruit TAMs to hypoxic GSC niches [3,17,19,33,94,97,99,100]. ECs secrete interleukin-6 (IL-6) in glioblastoma which can activate and attract TAMs into the tumor *via* HIF-2α-mediated arginase-1 expression and subsequently macrophage activation and glioblastoma progression [101]. OPN is strongly expressed adjacent to necrotic areas and blood vessels and colocalizes with CD68-positive macrophages and elastase-positive neutrophils [7,96]. Hypoxia also induces periostin expression by GSCs and TAM infiltration [100,102]. M-CSF and TGF-β released by GSCs induce M2-type polarization of TAMs [100,103]. TGF-β signaling between M2-type

macrophages and GSCs enhances invasive behavior of GSCs *in vitro* [103] whereas periostin can also enhance invasive behavior of glioblastoma cells *in vitro* [104]. It has to be elucidated whether the same mechanisms occur *in vivo* as well. GSCs secrete TGF-β1 and macrophage inhibitory cytokine as immunosuppressors [97], indicating that GSCs create their own niche. Interactions of GSCs and TAMs enhance glioblastoma progression [3,17,33]. Co-transplantation of TAMs and GSCs in immuno-deficient mice increased glioblastoma tumor growth [33].

GM-CSF expression is higher in GSCs than in differentiated glioblastoma cells [33]. Anti-GM-CSF antibodies inhibited TAM development in mouse models and consequently reduced tumor progression. Therefore, GM-CSF may be a candidate for therapeutic targeting of GSCs by disrupting their niches [33]. Finally, VEGF is not only expressed by GSCs but also by TAMs [17]. Expression of VEGF by TAMs suggests additional angiogenesis-promoting pathways in peri-immune niches as well as increased expression of niche factor SDF-1α and CXCR4 on GSCs [105,106].

TAMs are predominantly located in close vicinity of CD133-positive GSCs around blood vessels and in necrotic areas which enables interactions of TAMs and GSCs [17,37,97,99]. The amounts of TAMs found in peri-immune niches are correlated with glioblastoma progression [37,97,99] and inversely correlated with patient survival [36]. TAMs play a role in GSC invasion by production of high levels of TGF-β1 [22]. However, the exact role of TAMs in the maintenance of GSCs in a quiescent state remains to be elucidated.

3. An integrated concept of GSC niches

This is the first attempt, as far as we know, to compare and evaluate the different concepts of GSC niches. Comparison of the concepts of separate peri-vascular niches, peri-arteriolar niches, peri-hypoxic niches, peri-immune niches and ECM niches gave us the impression that each of the concepts is based on the perception of the niche from a specific point of view and that these different concepts can be integrated in one concept that describes one single type of niche: the hypoxic peri-arteriolar GSC niche. In this integrated concept, GSCs are localized in specific areas around the arteriolar adventitia which is a hypoxic environment. The arteriolar adventitia consists of ECM components, such as laminin, fibronectin and tenascin-C. Moreover, immune cells, such as TAMs, maintain GSC stemness by upregulating the expression of niche factors, such as SDF-1α and CXCR4. This hypoxic peri-arteriolar GSC niche is similar to the hypoxic peri-arteriolar compartment of the HSC niche in the bone marrow as we have recently proposed [79]. Three concepts of HSC niches have been described, but a critical evaluation of the concepts resulted in the concept of a single continuous hypoxic HSC niche with a peri-arteriolar compartment adjacent to the bone containing HSCs and a peri-sinusoidal compartment towards the center of the bone marrow where HSCs become progenitor cells that leave the bone marrow into the circulation [79]. In the peri-arteriolar compartment, the SDF-1α-CXCR4 and OPN-CD44 axes play a significant role in binding of CD133-positive HSCs in the niches. CatK is involved in hydrolysis of the SDF-1α-CXCR4 binding and releases HSCs out of niches [79]. Whether CatK and/or other proteases are involved in the hydrolysis of the OPN-CD44 binding has not been elucidated yet.

We have found exactly the same proteins to be localized in association with CD133-positive and nestin-positive GSCs in niches in glioblastoma. Moreover, all GSC niches that we found in tissue samples of human glioblastoma were adjacent to necrotic areas and a high expression of VEGF and HIF-1α was found around the necrotic areas that also included niches [7,9,31]. We did not find any niche around the 924 venules and 8085 capillaries and postcapillary venules that we checked in sections of 16 glioblastoma samples [9]. Sporadically, a number of the markers of GSC niches were expressed around larger venules but never all the markers at one time. Nevertheless, it may well be that peri-venular GSC niches exist in glioblastoma, but thus far we did not detect such niches yet. Because arterioles and venules are transport vessels and not exchange vessels like capillaries and postcapillary venules, the hypoxic and necrotic areas adjacent to the arterioles can be explained by the lack of oxygen in those areas despite the fact that oxygenated blood runs along in the lumen of the arterioles [107,108].

In our 2 studies [7,9], we have found only 9 and 7 niches in 5 and 16 glioblastoma samples, respectively. It is likely that sampling of the tumor tissue for our research has played a role in the search for niches, but we conclude on the basis of our 2 studies that niches are rather rare in glioblastoma. We found niches around only 2% of all arterioles in the glioblastoma sections that we investigated [7,9]. Vermeulen et al. (2012) reported that less than one GSC in every 1000 cells is found in glioblastoma [24]. This estimation and our semi-quantitative investigation are in agreement with each other.

In conclusion, peri-arteriolar and peri-hypoxic niches may well be 2 views at the same type of niche but from different angles. This can also be stated with respect to peri-immune niches that contain M2-type TAMs in close association with GSCs. We found in an earlier study co-localization of OPN and CD68-positive macrophages and/or elastase-positive neutrophils [96]. We also reported that leukocyte-related markers CD68, MMP-9, CD177 and neutrophil elastase were often but not always detected in OPN-expressing arteriolar GSC niches that also expressed SDF-1α [7]. The association between immune cells and GSCs in niches needs further analysis, but our studies indicate that peri-arteriolar, peri-hypoxic and peri-immune niches are 3 different views of one type of GSC niche from different perspectives.

The ECM niche is not a generally-accepted type of niche [16,35,38] but is often included in peri-vascular niches [19,46,67]. However, the ECM niche concept fits easily in the integrated peri-arteriolar, peri-hypoxic and peri-immune niche (Fig. 1). The wall of arterioles consist of the following layers from the lumen to the outer edge of the wall: endothelium, tunica elastica interna, tunica media, tunica elastica externa and tunica adventitia [107] (Fig. 2). We found GSCs in their niches that are attached to the outer rim of the tunica adventitia which consists of stroma that is ECM rich. Moreover, the tunica adventitia of human arterioles and venules contain mesenchymal stem cell (MSC) niches [109–113]. These niches are not in the same location as GSC niches. MSC niches are located in the adventitia close to the tunica media [110,111,114], whereas we found GSC niches at the outer rim of the adventitia [7]. The MSC niches contain malignant cells such as leukemic and glial stem cells [110,111,114]. Thus, further research is required to understand the relationship, if any, between GSC niches and MSC niches. However, it can be concluded that the ECM in the adventitia of arterioles (and possibly venules) is a microenvironment that is well suited for GSC niches. In bone marrow, MSCs are localized in the peri-arteriolar compartment as well as the peri-sinusoidal compartment of HSC niches, where MSCs express HSC maintenance factors such as SDF-1α, OPN, stem cell factor (SCF) and vascular cell adhesion molecule-1 (VCAM-1). In mice, depletion of MSCs resulted in mobilization of hematopoietic progenitor cells out of niches [79,80]. Thus, MSCs are crucial niche players in bone marrow for the maintenance of HSC stemness, but the exact localization of MSCs in HSC niches has not been determined yet as far as we know. The role of MSCs in peri-arteriolar GSC niches in unknown. The localization of MSCs in HSC niches in bone marrow, on the one hand, and the functional involvement of MSCs in GSC niches, on the other, are topics of our present investigations.

Finally, the peri-vascular niche concept fits also in the peri-arteriolar niche. The term peri-vascular does not discriminate between peri-arteriolar, peri-capillary, peri-venular and even peri-lymphatic. However, it is frequently assumed in the literature that peri-vascular means peri-capillary [29] which is not automatically correct. A number of studies of peri-vascular niches show histological or histochemical images [18,31,47,68,74,115,116]. In all cases, the blood vessels indicated as such show a size that is usually too large for capillaries, although sinusoid may have a widened lumen, and have walls that are far too thick for capillaries. Therefore, we like to stress that peri-vascular and peri-arteriolar (and possibly peri-venular) are not contradictory as

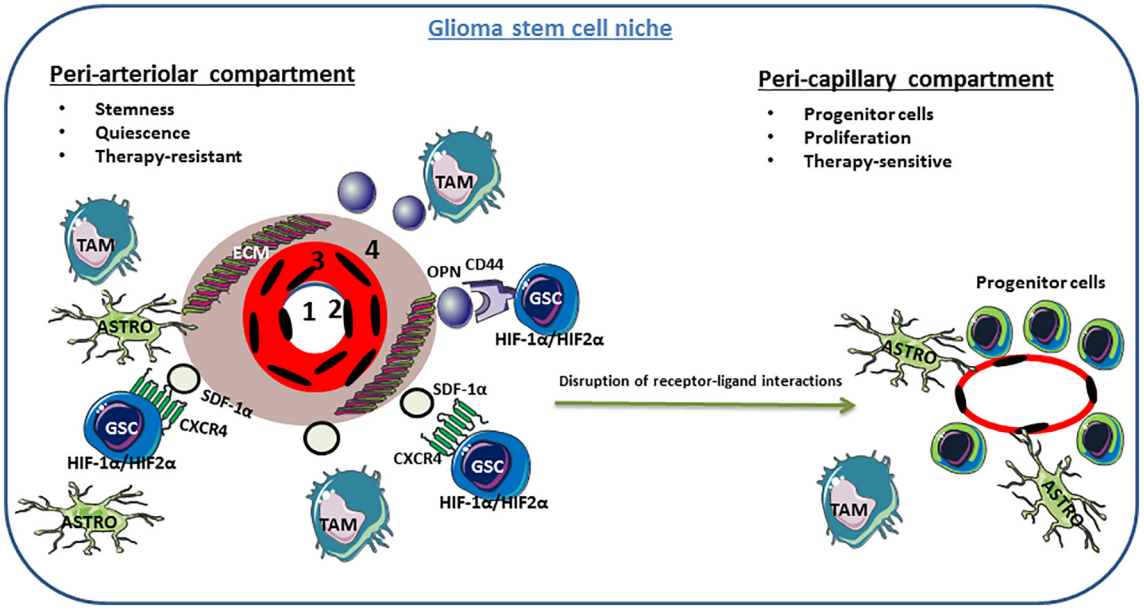

Fig. 1. Schematic representation of our concept of the hypoxic peri-arteriolar GSC niche. Therapy-resistant GSCs are localized at the outer rim of the arteriolar tunica adventitia which also contains ECM. Homing of GSCs in their niches is facilitated by SDF-1α/CXCR4 and OPN/CD44 interactions. HIF-1α and HIF-2α are expressed by GSCs due to hypoxic conditions. TAMs are involved in the maintenance of GSCs in the niches. Upon disruption of receptor-ligand interactions, GSCs differentiate into proliferative glioblastoma cells, which makes them more sensitive to chemotherapy and irradiation. 1 = lumen of arteriole, 2 = endothelial cell, 3 = smooth muscle cell, 4 = arteriolar adventitia. Abbreviations: ASTRO, astrocyte; CXCR4, C-X-C receptor type 4; ECM, extracellular matrix; GSC, glioma stem cell; HIF, hypoxia-inducible factor; OPN, osteopontin; SDF-1α, stromal-derived factor-1α; TAM, tumor-associated macrophage.

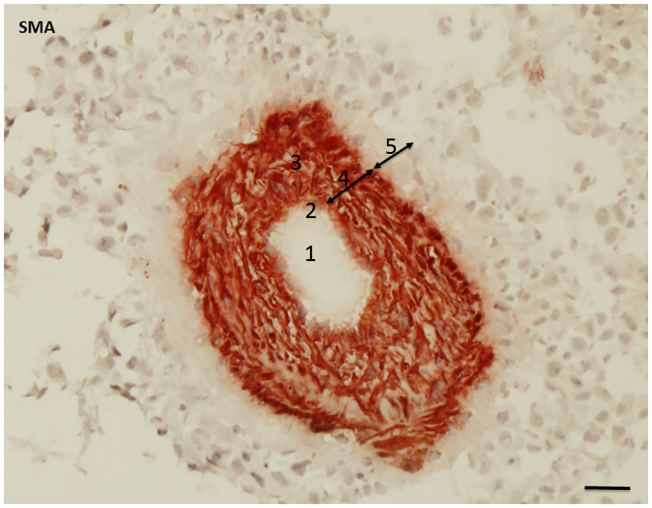

Fig. 2. Immunohistochemical staining of smooth muscle actin (SMA) in an arteriole in a glioblastoma tissue section. SMA is localized in smooth muscle cells (dark red). 1 = lumen of the arteriole, 2 = endothelial cell, 3 = smooth muscle cell, 4 = tunica media, 5 = tunica adventitia. Bar = 20 μm.

long as vascular is not taken for capillary [31].

In conclusion, the five types of GSC niches described are different views on one type of GSC niche, the hypoxic peri-arteriolar niche (Fig. 1). Our concept of the niche explains why both ECs and hypoxia are needed in GSC niches. Moreover, it is likely that the smooth muscle cells of the tunica media, the ECM and possibly cells present in the adventitia such as MSCs, fibroblasts and leukocytes, are important for conditioning the GSC niche.

4. Discussion

A series of studies have demonstrated that GSCs reside in specific microenvironments that affect and/or maintain their behavior in glioblastoma tumors. These niches are characterized by cells and proteins that are functional in interactions of GSCs with their niches [7,16–19,29,35,68]. The ultimate goal of the continuing investigations of these interactions between GSCs and their niches is to improve our understanding of how GSC niches mediate therapy-resistance, with the prospect of developing more effective therapeutic strategies against GSCs in glioblastoma.

In this study, we aimed to summarize all available literature on GSC niches in glioblastoma and we studied the type of blood vessels that are associated with GSCs in niches. Peri-vascular niches, peri-arteriolar niches, peri-hypoxic niches, peri-immune niches and ECM niches have been described in literature [3,7,16–19,29,32,35,36,68,117]. Tables 1 and 2 summarize the cell types and proteins involved in these niches and the cell biological functions of CD133-positive and nestin-positive GSC niche-associated proteins and markers. On the basis of this study and the studies by Hira et al. [7,9,31,62], we conclude that these five niches are not distinct from one another. The striking overlapping characteristics, proteins and cell types in the five niches suggest that there is one hypoxic peri-arteriolar GSC niche in glioblastoma. In fact, these GSC niches resemble HSC niches in bone marrow that are hijacked by acute myeloid leukemia cells that become quiescent and therapy-resistant leukemic stem cells (LSCs) in HSC niches [79,118,119].

When comparing peri-vascular niches, peri-arteriolar niches and peri-hypoxic niches, many similarities of the 3 types of niches become obvious. All three niches express the hypoxia markers HIF-1α and VEGF [7,16,32,46], but also SDF-1α and CXCR4 which are upregulated by HIF-1α and VEGF [105,106]. Expression of VEGF and HIF-1α are a result of a low oxygen microenvironment, as has been described for the peri-hypoxic niche [32,86], but their expression is also crucial in the peri-vascular and peri-arteriolar niche, since the SDF-1α/CXCR4 axis is important for the maintenance of GSC stemness [120]. In addition, the ECM niche is not a separate niche, since ECM is also present in the arteriolar tunica adventitia [107], which also supports our peri-arteriolar GSC niche concept. Based on the major similarities between the five niche types described in the literature so far, we suggest that these

niches are not five distinct niche types, but one single niche, the hypoxic peri-arteriolar GSC niche.

Glioblastomas have been classified into multiple subtypes. In 2010, Verhaak et al. showed that glioblastoma tumors can be classified into 4 subtypes; proneural, neural, classical and mesenchymal subtypes, where the proneural subtype has the most favorable patient survival and the mesenchymal subtype has the worst patient survival. Genetic aberrations of *EGFR*, *NF1* and *PDGFR/IDH* define classical, mesenchymal and proneural glioblastomas, respectively [121]. However, this classification is still under debate because of intratumoral heterogeneity which leads to the presence of multiple subtypes within one and the same tumor [122–124]. Until now, there is no profound evidence of different GSC niches in the different glioblastoma subtypes. Talasila et al. showed in 2016 that there are two main regions in glioblastoma tumors, invasive regions adjacent to blood vessels in normal brain tissue and angiogenic regions in the center of the tumor where hypoxia promotes angiogenesis [125]. We suggest that GSC niches are present in the angiogenic regions of glioblastoma tumors, where hypoxia maintains GSC stemness in peri-arteriolar niches.

4.1. Therapeutic strategies to target GSCs

We are convinced that a promising strategy to sensitize the quiescent GSCs to cytotoxic therapy is to disrupt the interactions between GSCs and their protective niches so that GSCs become differentiated proliferating glioblastoma cells that are more vulnerable to standard therapies (Fig. 1). GSCs express the receptors CXCR4 and CD44 to interact with their ligands and niche factors SDF-1α and OPN, respectively (Fig. 1), to retain in their niches [4,7,105,106,126]. Therefore, promising strategies to sensitize GSCs to chemotherapy and irradiation is to disrupt the SDF-1α/CXCR4 and OPN/CD44 axes. CXCR4 antagonists plerixafor/AMD3100 [127] or PRX177561 [128,129] can be used to inhibit the SDF-1α/CXCR4 axis. In addition, anti-CD44 antibodies may be promising to disrupt OPN/CD44 interactions [79]. This strategy is already used in clinical trials in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) patients. Phase I/II clinical trials in AML patients have shown that treatment with plerixafor in combination with chemotherapy gave a better overall complete response rate (46%) as compared to chemotherapy alone (21%). This improved response rate was achieved due to a 2-fold increase in mobilization of CXCR4-positive LSCs out of HSC niches, their differentiation and subsequently sensitization to chemotherapy [79,130]. OPN can also facilitate homing of CD44-postitive LSCs in HSC niches. Therefore, a phase I clinical trial is ongoing in AML patients, using RG7356, an anti-CD44 antibody [131]. Our ultimate aim is to implement similar therapeutic strategies in glioblastoma patients with the aim to enforce GSCs out of their protective niches to target them more efficiently with chemotherapy and irradiation.

5. Conclusions

The major conclusion of this study is that the five GSC niche types in glioblastoma described in literature, the peri-vascular niche, the peri-arteriolar niche, the peri-hypoxic niche, the peri-immune niche and the ECM niche, can be integrated into one single niche type: the hypoxic peri-arteriolar GSC niche. In addition, hypoxic peri-arteriolar GSC niches are structurally and functionally look-alikes of HSC niches in the bone marrow. This concept should be rigidly tested in the near future to develop therapies to expel GSCs out of their protective niches to render them more vulnerable to standard therapies.

Transparency document

The Transparency document associated with this article can be found, in online version.

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