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Editorial Open Access

Impact of Microenvironment in Therapy-Induced Neovascularization of Glioblastoma

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Abstract

Therapy induced neovascularization is an emerging cancer hallmark, which has been observed during the antiangiogenic treatments (AATs) to suppress angiogenesis in glioblastoma and other cancers. Clinicians and researchers have following major questions such as (1) why the AATs are inducing unwanted vasculature? (2) What are the molecular mechanisms associated with this daunting outcome? (3) What are signature targets to combat tumor angiogenesis or vasculogenesis? Focused strategies to investigate these aforementioned questions are required to answer to proceed further. Recent studies have shown the importance of microenvironment in the regulation of angiogenesis and/or neovascularization both at cellular and molecular levels. Better agents with broad range of targets could help to reprogram the tumor microenvironment as well as to combat the tumor and therapy induced neovascularization.

Editorial

Despite optimal treatments and evolving standard care, the median survival of patients diagnosed with WHO grade IV gliomas i.e. glioblastoma (GBM) is only 12 to 15 months [1]. GBM is highly vascularized cancer, which is considered as most lethal during the first year after initial diagnosis despite resection and radiotherapy and/or chemotherapy [1]. Higher micro vessel density in GBM is significantly correlated with the worst prognosis and is therefore a target for antiangiogenic therapy (AAT) [2,3]. Given the importance of VEGF pathway in neovascularization, several approaches have been developed to suppress VEGF signaling [4]. Surprisingly, it resulted to an enhanced vasculature and invasive tumor phenotype in GBM [5,6]. In addition, anti-VEGF therapy induced hypoxia inducible factor 1 alpha (HIF1-α) expression in GBM patients [7] as well as in mice models of glioma [8]. Several AATs showed no to minimal effect [9-11], when targeting VEGFR tyrosine kinase activity using cediranib, sunitinib, and imatinib tested in GBM patients [2]. Vatalanib treatment induced over-expression of VEGF as well as the Flk-1/VEGFR2 receptor tyrosine kinase, especially at the rim of the tumor in rat model [12]. These findings provided direct evidence that VEGF can act as a negative regulator of tumor neovascularization.

In GBM tumor, vessels are tortuous, disorganized, highly permeable, and have abnormal endothelial cells (ECs), pericyte coverage, and basement membrane structure [2,13]. There is a known heterogeneity of vasculature development in tumor condition. Conventionally, tumor vessel formation occurs through angiogenesis, which is mediated by proliferation and migration of resident ECs [14]. Instead, vasculogenesis originates from circulating bone marrow derived endothelial progenitor cells (EPCs), which express VEGF receptor 2 (VEGFR2), are recruited by VEGF followed by differentiation and incorporation into new tumor blood vessels [15]. In addition, hypoxia is a common feature of GBM, which is involved in EPCs recruitment through up-regulation of HIF1-α, induction of stromal cell derived factor-1 alpha (SDF1α), secretion of various proangiogenic factors and recruitment of bone marrow derived cells (BMDCs) or EPCs due to presence of CXCR4 receptors on EPCs [16-18]. Depending on tumor development, neovascularization occurs by alternate mechanisms such as vascular mimicry [19,20] and vascular transdifferentiation from glioma stem cells [21,22]. On the contrary, glioma stem cells rather form pericytes instead ECs [23]. Interestingly, tumor cells that functionally participate in the vessel lining are detected rarely in human GBM [24] and, therefore, it reduces the significance of vascular transdifferentiation over other dominant mechanisms such as vasculogenesis through BMDCs. However, detailed molecular mechanisms of regulation of BMDCs in vasculogenesis are poorly studies at cellular and molecular levels.

Previously, tumor was considered as single entity, however, uncontrolled interaction between tumor cells and associated stroma is critical in tumor microenvironment for initiation and progression of cancer [25]. Similarly, each cancer hallmark such as angiogenesis or neovascularization is regulated by interaction of microenvironment through series of steps [26]. Recently, experimental studies have shown the emerging role of microenvironment in GBM development. For example, chemo attractant signaling through tumor cells secreted CSF-1 recruit macrophages and regulate neovascularization at the tumor periphery, which is rich in angiogenic factors [27,28]. Similarly, recurrent GBM showed an increased infiltration in myeloid populations in the tumor bulk and in the infiltrative regions after AAT. Higher numbers of CD11b+ cells correlated with poor survival among these patients. These data suggest that tumor-associated macrophages may participate in escape from AAT [29], represent a potential biomarker of resistance and a potential therapeutic target in recurrent GBM [29]. However, more studies are required to understand the mechanism of this relapse during AAT, which is associated with increase EPCs/BMPCs and macrophage recruitment/polarization at cellular level.

At the molecular level, release of soluble cytokines and chemokines are recognized as the classical mechanisms underlying cell-to-cell communication within the tumor microenvironment [30]. Recent

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findings on vesicle-based signaling by exosomes (30–100 nm) are recognized as a novel mode of cell–cell communication during tumor progression [31]. Exosomes are the luminal membranes of the late endosomes/ multi-vesicular bodies, which released from the cell membrane of donor cells and binds to recipient cells [32]. Exosomes are also released from the surface of normal healthy cells as a physiological phenomenon. However, number of exosomes release increases upon cell activation, hypoxia, irradiation, injury, exposure complement proteins, and as a result of cellular stress [31]. Exosomes are now considered biologically active entities that perform a variety of extracellular functions including interactions with the cellular microenvironment, such as immunological activation, cell recruitment, transfer of genetic material and thus consider as bona fide secreted factor [32,33]. Since, the hypoxia is a characteristic feature of GBM; secreted exosomes reflect hypoxic status of the tumor cells. Exosomes are enriched in several hypoxia-regulated proteins such as matrix metalloproteinase 9 (MMP9), pentraxin 3 (PTX3), IL8, PDGFAB/ AA, CD26, caveolin 1 (CAV1), and plasminogen activator inhibitor 1 (PAI1) [34]. Kucharzewska et. al, reported that expression of these factors was correlated with significantly enhanced tumor vascularization due to paracrine activation of ECs by tumor cell secreted exosomes and autocrine tumor growth under hypoxic condition [34]. However, authors failed to report the effect of AAT on hypoxia-regulated exosomes and their role in promotion of neovascularization in GBM. In addition, hypoxia was shown to induce specific miRNA signatures [35-37]. Therefore, it will be interesting to investigate if hypoxia could be the inducer of miRNA processing and export through exosomes, which needs to be investigated using AAT in GBM.

Given the aforementioned limitations in targeting candidate molecule/ pathway in GBM, such as anti-VEGF therapy suggests that tumor-induced neo-vasculaization is intricate and needs special agent, which has broad effect. MiRNAs have been shown to display broader range of targets because of partial to complete gene sequence homology of miRNA with target; therefore, a single miRNA could have hundreds of targets and regulate diverse cellular pathways. Since the miRNA-based therapeutics in cancer is growing [38-40], investigations for signature micro RNAs are required in GBM tumor. Alteration of discovered signature miRNAs will provide the opportunity to treat the GBM by reprogramming of tumor microenvironment due to broad effect of miRNA over other available antiangiogenic drugs. In conclusion, investigation of role of microenvironment both at cellular and molecular levels could provide better understanding of therapy induced vasculature development and hence answer to the current clinical trials and treatment strategies in patients with GBM.

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