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Antiangiogenic Therapy for Malignant Brain Tumors: Does It Still Matter?

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Abstract

Purpose of Review To summarize the mechanisms of tumor angiogenesis and resistance to antiangiogenic therapy, and the influence on tumor microenvironment.

Recent Findings Several clinical trials have investigated the activity of anti-VEGF monoclonal antibodies and tyrosine kinase inhibitors in glioblastoma, shedding the light on their limitations in terms of disease control and survival. We have outlined the mechanisms of resistance to antiangiogenic therapy, including vessel co-option, hypoxic signaling in response to vessel destruction, modulation of glioma stem cells, and trafficking of tumor-associated macrophages in tumor microenvironment. Moreover, novel generation of antiangiogenic compounds for glioblastoma, including small interfering RNAs and nanoparticles, as a delivery vehicle, could enhance selectivity and reduce side effects of treatments.

Summary There is still a rationale for the use of antiangiogenic therapy, but a better understanding of vascular co-option, vascular mimicry, and dynamic relationships between immunosuppressive microenvironment and blood vessel destruction is crucial to develop next-generation antiangiogenic compounds.

Keywords Antiangiogenic therapy · Bevacizumab · Glioblastoma · High-grade glioma · Tyrosine kinase inhibitors

Introduction

Angiogenesis is the growth of new blood vessels, which is typical of high-grade gliomas (HGG) and glioblastomas (GBM), the most common primary malignant brain tumors in adults. The heterogeneous histopathologic appearance of GBM includes extensive proliferation of endothelial cells (EC), with glomeruloid vessel–like structures, that are supported by basal lamina and pericytes with a lack of astrocytic end-feets. Thus, given the poor prognosis of GBM following surgery and radiotherapy with concomitant and adjuvant chemotherapy with temozolomide [1, 2], antiangiogenic therapy has been the most investigated strategy for GBM in the last decade. In this regard, the human monoclonal antibody (mAb) bevacizumab (Bev), that targets vascular endothelial growth factor (VEGF)-A, achieved the approval by the US Food and Drug Administration (FDA) for the treatment of GBM at first relapse after the standard chemoradiation based on the prolonged progression-free survival (PFS) and clinical benefit, such as relief of neurological symptom and reduction of steroids [3–5]. However, Bev did not prolong overall survival (OS) in patients with newly diagnosed or recurrent GBM in phase 3 clinical trials [5–7]. Nevertheless, a rationale for targeting neoangiogenesis still matters, since angiogenesis influences the immunosuppressive tumor microenvironment (TME) in GBM. Hence, reducing the angiogenic pathways in the TME could increase antitumor immune response. On the other hand, the significant reduction of tumor vasculature following antiangiogenic therapy causes hypoxia, leading to activation of alternative pathways to maintain tumor angiogenesis [8, 9]. Moreover, glioma neoangiogenesis results in tortuous blood vessels, that interfere with the blood–brain barrier (BBB)

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permeability [10], resulting in unequal drug distributions into brain tumors [11, 12].

Angiogenesis and Mechanisms of Resistance to Antiangiogenic Therapy

Several cellular and molecular mechanisms are involved in tumor angiogenesis. The rapid tumor proliferation causes severe hypoxia and nutrient deprivation, and enhances the production of angiogenic cytokines and matrix metalloproteinases (MMP) by TME, causing an activation of EC, pericytes, reactive astrocytes, tumor-associated macrophages (TAM), and neoplastic cells. This pro-angiogenic and pro-inflammatory TME favors the formation of leaky and abnormal blood vessels, that are not able to efficiently deliver nutrients, oxygen, and drugs.

Glioma stem cells (GSC) create tube-like structures devoided of vascular EC and containing red blood cells, therefore known as vasculogenic mimicry (VM). These vascular structures may merge with micro-vessels formed by angiogenesis to support blood and nutrient supply, as well as favor the passage of glioma cells directly into the bloodstream. Different key players from TME trigger the VM, such as HIF1a, epithelial-mesenchymal transition (EMT), and VE-cadherin/EphA2/MMP signaling pathways, that enhance the hypoxic environment, while adenosine/STAT3/IL-6 pathway, MAPK/ERK pathway, Wnt/b-catenin, Notch, Wnt, Hedgehog, and Hippo signaling pathway are primarily involved in increasing the GSC pool [13, 14].

Pro-angiogenic and pro-inflammatory cytokines, including HIF1a, VEGF, IL6, and CX3CL1, induce the infiltration and differentiation of bone marrow–derived mesenchymal cells (BM-MC) into macrophages and pericytes, that modulate the balance between pro- and antiangiogenic cytokine production, and enhance the EC survival.

Activation of COX2 results in an overexpression of prostaglandin E2 (PGE2), thromboxane A2 (TXA2), and prostaglandin I2 (PGI2), that increases migration, sprouting, and proliferation of EC and glioma angiogenesis. Notably, the interaction of epidermal growth factor receptors (EGFR) with signal transducer and activator of transcription 3 (STAT3) or the constitutive activation of EGFR variant III/STAT3 pathway enhances the COX2 signaling and favors glioma angiogenesis.

Overexpression of some tyrosine kinase receptors is involved in glioma angiogenesis, such as VEGF receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), and Eph receptors. VEGFR-2 and VEGFR-3 guide neoangiogenesis for blood and lymphatic vessels, respectively, while VEGFR-1 inhibits neoangiogenesis. The PDGFR regulate pericytes and smooth muscle cells activity to stabilize vascular wall, and Eph receptor defines arterial or venous identity. Additionally, the overexpression of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)-Akt pathways supports angiogenesis, tumor proliferation, and escape from apoptosis [15].

Although targeted therapy with mAbs or tyrosine kinase inhibitors (TKIs) may provide a transient period of normalization of tumor vasculature, different mechanisms of resistance to antiangiogenic therapy have been identified. Compensatory angiogenic signaling is activated by means of HIF1a, Notch, and Ang2/Tie2 signaling pathways within the hypoxic GBM TME. An immunological escape may occur: monocytes, TAM, reactive astrocytes, myeloid cells, neutrophils, and T helper-17 cytokines promote the infiltration of the pro-angiogenic clones of BM-MC resulting in tumor angiogenesis.

An increased pericyte coverage after antiangiogenic therapy contributes to sustain the survival of EC. Vessel co-option consists in the migration of tumor cells toward and along the preexisting vasculature. Typically, a subset of GSC with pericyte differentiation under the production of bradykinin/bradykinin receptor-2 (B2R), CXCR4/SDF-1a, MDGI/FABP3, EGFRvIII, and Olig2/Wnt7a increase pericyte coverage in the co-opted blood vessels and support survival of EC by promoting an autocrine VEGF-A signaling pathway [16, 17]. Autophagy provides energy for neoplastic cells to survive under hypoxic conditions through HIF-1-dependent mechanisms.

Clinical Trials on Antiangiogenic Monoclonal Antibodies (mAbs) in GBM

Overall, the main aim of antiangiogenic treatment for GBM is to regulate the permeability of tumor vasculature and reduce the growth of new tumor vessels. When the permeability of BBB is normalized, a more effective delivery of antineoplastic compounds with adequate CNS concentrations should be achieved. An ideal antiangiogenic drug should meet some characteristics, such as high selectivity, targeting multiple signaling pathways, low risk of drug-induced resistance, enhancing the production of endogenous antiangiogenetic molecules, and limited systemic toxicity.

Antiangiogenic mAbs have been investigated in several clinical trials, showing some activity in terms of PFS, but disappointing results regarding OS. Bev, a human monoclonal antibody, which binds circulating VEGF-A, conferred an advantage in 6-month PFS when associated with irinotecan (50%) as compared with Bev alone (42%) in the BRAIN trial [3], leading to the approval by FDA for the use at first recurrence. Similarly, in Europe, the BELOB trial has shown encouraging results for the combination of Bev and lomustine versus either agent alone [18]. However, the phase 3 trial investigating the combination of

Bev plus lomustine in comparison with lomustine alone failed to demonstrate an improvement of OS (median OS 9.1 months versus 8.6 months) despite an increase of PFS from 1.5 to 4.2 months [5]. Other phase 2 trials have investigated Bev in association with several drugs, including temozolomide, fotemustine, irinotecan, temsirolimus, and erlotinib, but none has displayed a significant impact on OS [19–22]. Although some concerns regarding fertility arise when Bev is used in patients with GBM at childbearing ages, in general it is well tolerated and serious adverse events, such as gastrointestinal perforation, thromboembolic events, renal injury, impairment of wound healing process, posterior reversible encephalopathy syndrome, congestive heart failure, and uncontrolled hypertension, are rare. A post hoc analysis of the ARTE trial has shown a survival benefit from the addition of Bev to radiotherapy in comparison with Bev alone in elderly patients with newly diagnosed GBM. This effect could depend on the presence of large contrast-enhancing lesions, while the detection of non-contrast-enhancing tumor on amino acid PET scans was associated with inferior survival. These findings suggest that Bev may work as a radiosensitizer in presence of dysfunctional vasculature in GBM [23, 24]. Some preclinical and translational studies have displayed that the effect of VEGF-targeted therapy on tumor barrier permeability is transient and dose-dependent [25, 26]. Notably, lower doses (< 10 mg/kg) of Bev may induce reduction of leakiness, improve oxygenation without inducing vessel destruction, and favor the up-regulation of angiopietin-2 (Ang-2), a potent driver of vessel leakiness [27]. Hence, low dose of VEGF-targeted therapy in association with Ang-2-targeted treatment has been proposed to overcome resistance to antiangiogenic therapies by regulating GBM barrier permeability and modulating the pro-tumorigenic effects of endothelial cell destruction [28]. The Ang-2 neutralizing antibody MEDI3617 was evaluated in combination with Bev in a phase 1b study in 116 patients with solid tumors, including 13 GBM patients, but unfortunately showed a poor activity (0% of radiological response in GBM) [29].

Aflibercept is a recombinant human fusion protein, that acts as a soluble decoy receptor for VEGF-A, VEGF-B, and placental growth factor, thus depleting circulating levels of these growth factors. A phase 1 trial suggested that aflibercept in combination with temozolomide could confer moderate toxicities, including fatigue, hypertension, lymphopenia, ischemic stroke, and systemic hemorrhage. All patients stopped the treatment: 28 (47%) for disease progression, 21 (36%) for toxicities, 8 (14%) for other reasons, and 2 (3%) patients only completed the full treatment course [30]. The phase 2 trial reported limited efficacy of aflibercept in both grade 3 astrocytomas (radiological response in 44%, 6-month PFS of 25%, median PFS of 24 weeks) and GBM (radiological response in 18%, 6-month PFS of 7.7%, median PFS of 12 weeks) [31].

Tanibirumab is a fully human monoclonal antibody targeting soluble VEGFR-2, that was investigated in a phase 2 trial in 12 patients with recurrent GBM. The best radiological response was a stable disease in 3/12 (25%) patients of whom 2 patients had a long-lasting response of 60 and 40 weeks, respectively, and was correlated with the highest expression of VEGFR2 using immunohistochemistry on archival tumor [32].

Preclinical data on targeting VEGFR2 are emerging. Chen et al. have shown that the anti-VEGFR2 mAb MSB0254 inhibits the invasion and migration of U251 and primary glioma cells in vitro. Moreover, MSB0254 also significantly inhibits the expression of CD34, VEGFR2, Ki67, MMP2, and MMP9 and reduces the VM formation, resulting a compound to be further investigated for the treatment of GBM [33•].

As VEGF-targeted mAbs have failed to control disease in GBM, we argue that vascular normalization is not the sole factor to overcome treatment resistance of GBM, and other mechanisms may co-exist or even prevail upon targeting neoangiogenesis.

Targeting Vessel Co-option

Wnt-7 has been identified as a driver of vessel co-option in a subpopulation of GSC with features of oligodendrocyte precursor cells. Wnt-7 is secreted by the membrane-bound O-acyl transferase porcupine, that can be targeted by the BBB penetrating small molecule inhibitor LGK974. In a glioblastoma xenograft model, LGK974 reduced vessel co-option and VEGF expression, but data on clinical activity on human GBM, as well as the ability to cross the BBB, are lacking [34••, 35]. CXCR-4 positive GSC are up-regulated following Bev [36] and can be targeted by the small molecular CXCR4 inhibitor, plerixafor. In a phase 1 trial of plerixafor with Bev in patients with recurrent HGG, remarkable concentrations of the small molecular inhibitor were identified in the CSF and brain tumor tissue, as well as biomarker changes consistent with VEGF and CXCR-4 inhibition. Unfortunately, despite the demonstration of adequate drug penetration and downstream effects, the efficacy of this combination in disease control was limited [37]. The mammalian target of rapamycin (mTOR) promotes anabolic metabolism of GSC, invasiveness, and poor sensitivity to chemo- and radiotherapy [38]. However, the mTOR inhibitor temsirolimus failed to prolong OS when associated with radiotherapy versus radiotherapy plus temozolomide in patients with newly diagnosed unmethylated O6-methylguanine-O-methyl-transferase (MGMT) GBM. Interestingly, a small subgroup of patients with Ser2448 phosphorylation

of mTOR derived a strong benefit from temsirolimus [39]. Whether temsirolimus may overcome resistance to Bev by specifically targeting GSC has not been studied thus far.

In summary, some preclinical studies suggest that targeting vessel co-option could provide a synergic activity with antiangiogenic therapy, but efficacy of such an approach is far to be demonstrated.

Co-regulation of Angiogenesis and Immunosuppressive TME in GBM

Tumor microenvironment of malignant gliomas is immunologically "cold" as it is dominated by immunosuppressive and pro-angiogenic cells, including 80% of macrophages, monocytes, and neutrophils, with < 10% of dendritic cells, T cells, and natural killer cells [40]. Furthermore, tumor-derived soluble factors contribute to the immunosuppressive microenvironment [41•]. In this regard, interferon (IFN)-γ or lipopolysaccharide promotes a pro-inflammatory phenotype of macrophages (phagocytic "M1"), while autocrine and paracrine stimulation by IL-4, IL-6, IL-10, or TGF-β induce an immunosuppressive "M2" phenotype of macrophages. Importantly, hypoxia and HIF-1 favor M2-polarization of perinecrotic macrophages in experimental gliomas [42, 43]. VEGF exerts an immunosuppressive activity by inducing down-regulation of antigen presentation through the inhibition of dendritic cell maturation: involved mechanisms are the inhibition of nuclear factor-κB (NF-κB), and up-regulation of PD-L1 on myeloid and endothelial cells, that lead to inhibition of T cell extravasation and activation, inhibition of T cell differentiation in the thymus, expansion of inhibitory regulatory T cells (Treg), and inhibition of cytotoxic CD8 + T effector cells, such as PD-1, CTLA-4, T cell immunoglobulin mucin receptor 3 (TIM3), and lymphocyte activation gene 3 protein (LAG3).

TGF-β has been considered a master of immunosuppression of TME, but inhibiting TGF-β signaling with the targeted therapy with galunisertib was unsuccessful in a phase 2 clinical trial in patients with GBM [44]. Moreover, the combination of galunisertib with anti-VEGF treatment did not confer any significant benefit [45].

VEGF and hypoxia can drive the expression of chemoattractants, such as the CC-chemokine ligand 2 (CCL-2), via CC-chemokine receptor 2 (CCR2) and CCR4, leading to a higher level of CSF-1, that stimulates a subpopulation of pro-angiogenic macrophages expressing the Ang-2 receptor Tie-2, and co-opts micro-vessels and enhances M2 macrophages [46, 47]. The small molecule CSF-1 R inhibitor BLZ945, which is a CSF-1 R inhibitor, can enhance a pro-inflammatory M1 phenotype of macrophages and prolong survival in platelet-derived growth factor (PDGF)–driven genetic glioblastoma models, as well as reduce VEGF-driven proliferation of macrophages. In this regard, a phase 1/2 trial of BLZ945 in association with the PD-1 antibody spartalizumab in solid tumors, including GBM, has completed the enrollment in December 2022, and the analyses for the primary outcomes (dose-limiting toxicities, maximum tolerated dose, incidence of adverse events, and PFS) are ongoing (NCT02829723).

The low mutational burden and the immunosuppressive TME explain the failure of anti-PD1 compounds in phase 3 clinical trials on GBM [48]. However, some lymphocyte-independent macrophages can be stimulated by targeting the PD-1 pathway [49], and be active also in genetic glioblastoma models with low antigen expression [50]. Notably, the use of an oncolytic virus, designed to reprogram macrophages, induced an up-regulation of VEGF; thus, the administration of a VEGF antibody enhanced the antitumor activity of viral therapy [51]. Similar results were reported by Saha et al. who demonstrated that T cell–independent cooperation can be increased by a viral therapy in combination with the VEGF inhibitor axitinib in a transplantation-based hypoimmunogenic glioblastoma model [52], supporting the concept that targeting VEGF can support macrophage repolarization.

Although preclinical and clinical studies have shown the feasibility of chimeric antigen receptors (CAR) T cell immunotherapeutic approach in GBM, tumor heterogeneity, and antigen loss remain one of the upmost challenges to be addressed. Rousso-Noori et al. have identified the p32/gC1qR/HABP/C1qBP as a specific tumor-associated antigen expressed on the surface of glioma cells, resulting a feasible target for CAR T cell therapy with ability to control tumor growth in orthotopic syngeneic and xenograft mouse models. Therefore, further investigation on such a dual antitumor and antiangiogenic p32 CAR T cells will be warranted [53••].

Vascular Characteristics Among Glioma Subtypes

Proneural GBM has been reported to express a predominance of vascular co-option [34••], while mesenchymal GBM has a higher abundance of macrophages, vascular abnormalities, hypoxia, and necrosis [54]. The post hoc analyses of the phase 3 AVAglio trial on radiation plus temozolomide with versus without Bev reported an OS advantage for the proneural GBM [55]; however, such an association was not confirmed in other studies [23, 56].

The vasculature of IDH-mutated GBM has a lower frequency of vascular abnormalities and necrosis as compared with IDH wild-type GBM [57]. The F3 gene, which encodes the key prothrombotic protein tissue factor, is downregulated in IDH-mutated GBM [58], resulting in an increased cerebral blood flow [59], reduced angiogenesis, and abnormal tumor vasculature due to the inhibition of mesenchymal

GSC phenotypes [60]. Furthermore, IDH-mutated GBM escape from adaptive immunity by down-regulating major histocompatibility complex I to prevent antigen presentation by tumor cells [61], and suppressing chemotaxis-associated gene expression programs for T cell activity [62]. IDH inhibitors stimulate T cell infiltration and activity of a peptide vaccine against IDH-mutated gliomas in vivo [62, 63]: however, the influence on the altered vasculature remains unknown. In a phase 2 clinical trial of Bev in combination with temozolomide compared to temozolomide alone in IDH-mutated astrocytic brain tumors, no efficacy of Bev was observed [64].

Clinical Trials of Antiangiogenic Tyrosine Kinase Inhibitors in GBM

Axitinib is an oral small multi-TKIs targeting VEGF1-3, c-KIT, and PDGFR, that was investigated in different clinical trials, showing frequent grade 3/4 adverse events, including fatigue, diarrhea, and oral hyperesthesia. In a phase 2 trial in recurrent GBM, axitinib showed an ORR and 6-month PFS of 28% and 34%, respectively, as compared with 23% and 28% of patients treated with Bev or lomustine [65]. Another phase 2 trial has investigated whether the association of axitinib and lomustine could improve ORR and PFS in recurrent GBM, but the combination therapy did not show any advantage compared with axitinib alone (ORR 38%, 6-month PFS 17%, OS 27.4 weeks in the axitinib plus lomustine arm; ORR 28%, 6-month PFS 26%, OS 29 weeks in the axitinib arm) [66]. Unfavorable results of another phase 2 trial on the efficacy and tolerability of axitinib plus avelumab led to a discontinuation of further investigations [67].

Cabozantinib is a multi-kinase inhibitor of VEGFR2, c-MET, AXL, and RET, which was evaluated in a phase 1 trial in association with chemoradiation in newly diagnosed GBM, showing a manageable profile [68], and is under investigation in association with the anti-PD-L1 atezolizumab in a phase 1/2 clinical trial on recurrent GBM (NCT05039281).

Nintedanib is an oral, small-molecule TKI of PDGFR α/β, FGFR 1–3, and VEGFR 1–3, that may overcome resistance to anti-VEGF therapy. Although nintedanib was well tolerated, two different trials did not display any activity against recurrent GBM regardless of prior Bev therapy [69, 70].

Regorafenib is an oral inhibitor of several kinases involved in tumor angiogenesis (VEGFR1-3 and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF), and in the interaction between tumor and microenvironment (PDGFR, FGFR), and tumor immunity (colony-stimulating factor 1 receptor [CSF1R]). In the randomized, open-label, phase 2 REGOMA trial, GBM patients at first recurrence were treated with either regorafenib or lomustine displaying an OS of 7.4 vs 5.6 months, as well as 6-month PFS of 16.9% vs 8.3%, respectively [71]. Of note, the OS of patients treated with lomustine from REGOMA trial was remarkably short (5.6 months) as compared with that of patients included in the lomustine single arms of other randomized controlled trials (median OS 7.1–10.4 months [5, 72, 73], which could imply an overestimation of regorafenib efficacy. Few other studies have shown similar impact on survival [74–79], but a higher rate of adverse events than in REGOMA, thus raising concerns over tolerability. A lower intensity regimen proved as effective as the standard 160 mg daily schedule used in REGOMA trial (median PFS and median OS of 2.0 months and 7.4 months), but with lower adverse events [80]. The AGILE trial (NCT03970447) will help to clarify the role of regorafenib in patients with newly diagnosed GBM without MGMT promoter methylation.

Other VEGF multi-kinase inhibitors have been evaluated in recurrent GBM, such as sunitinib, sorafenib, ponatinib, and vandetanib, and all showed minimal or absent activity or raised major concerns for serious adverse events [81•].

Conclusions

Angiogenesis is a crucial mechanism for tumor cell survival, providing nutrients and oxygen, and promotes tumor immunosuppression. Significant efforts have been made to develop and evaluate the efficacy of novel antiangiogenic drugs for HGG, especially mAbs and drugs. The efficacy of an anti-VEGF mAb presents different barriers, ranging from low penetration into tumor tissue to failure to adequately cross the BBB due to the large size of the compounds. Conversely, TKIs have smaller size and target angiogenesis via different pathways but have low selectivity resulting in major systemic toxicities, as well as increased risk of acquired resistance.

Next-generation antiangiogenic therapies aim to overcome these limits. In this regard, small interfering RNA (siRNAs) are potent effective silencers of tumor angiogenic gene expression in GBM when loaded in tumor-targeted nanoparticles. These compounds display several advantages, including minimal recognition by the immune system, blood stability, high specificity, and low systemic side effects [82•]. Hence, nanotechnology is working on the development of novel delivery systems that can improve delivery of siRNAs and protect them from degradation and systemic clearance. To date, two different studies have explored carriers for siRNA delivery in GBM. A phase 1 study examined the side effects and best dose of DOPC-encapsulated EphA2 siRNA in the treatment of patients with metastatic solid tumors or recurrent GBM and demonstrated that this compound is able to slow the growth of tumor cells (NCT01591356). Another phase 0 study has evaluated a potential treatment for

GBM with the use of RNA-interfering spherical nucleic acids (SNAs), that consist of nuclei of gold nanoparticles covalently bonded to Bcl2L12 siRNA oligonucleotides, that can penetrate the brain. In this study, patients with recurrent GBM were treated with intravenous administration of siBcl2L12-SNAs revealing remarkable gold enrichment in the tumor-associated endothelium, macrophages, and tumor cells, as well as reduction in tumor-associated Bcl2L12 protein expression [83••]. Overall, numerous nanoplexes are being tested in preclinical setting, and could serve as potential next-generation antiangiogenic therapeutics for GBM [84–88].

Lastly, it is unclear whether and how antiangiogenic therapy and immunotherapy should be combined with radiotherapy and/or chemotherapy. Given that radiotherapy may favor antigen release from tumor cells, apoptosis of EC, and promote the influx of monocytes into TME, the combinations with immunotherapy and antiangiogenic therapy may enhance this effect and should be evaluated preclinically in the context of current standard treatments.

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Declarations

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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