Glioblastoma (GBM) is the most lethal primary brain tumor of the central nervous system in adults [1]. Despite the availability of multidisciplinary treatment including surgery, chemotherapy, radiation therapy, and tumor-treating fields therapy, the prognosis of GBM is still dismal, with a median overall survival of less than two years [2-4]. Several clinical trials have been conducted on treatments for GBM, including molecular targeted therapy and immunotherapy, but the antitumor effects observed in these trials have been limited and these treatments have not improved survival [5-9]. GBMs often change their biological characteristics during progression and recurrence, and intra- and inter-tumor heterogeneity is recognized as one of the crucial factors hindering the therapeutic progress of GBM [10,11].

To better understand the determinants of GBM heterogeneity and treatment resistance, numerous studies have been conducted to classify and characterize the molecular background of GBM on the basis of clinical, genomic, and transcriptomic features. Phillips et al. pioneered the definition of three signatures of GBM on the basis of gene expression: the proneural, classic, and mesenchymal subtypes. The mesenchymal subtype is the most aggressive, and patients with the mesenchymal subtype of primary and recurrent tumors tend to have a worse prognosis compared with patients with the other subtypes. Furthermore, GBM can shift from other subtypes to the mesenchymal subtype over the course of disease progression or recurrence. This phenotypic transition is driven by diverse tumor-intrinsic molecular mechanisms or microenvironmental factors. Thus, better understanding of the plastic nature of mesenchymal transition in GBM is pivotal to developing new therapeutic strategies. In this review, we provide a comprehensive overview of the current understanding of the elements involved in the mesenchymal transition of GBM and discuss future perspectives.

Key words: glioma, glioblastoma, mesenchymal subtype, mesenchymal transition, heterogeneity

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express genes related to cell proliferation and angiogenesis, and elderly patients with these subtypes show a poor prognosis [12]. The Cancer Genome Atlas (TCGA) Research Network identified four transcriptomic subtypes of GBM (proneural, neural, classical, and mesenchymal) on the basis of unsupervised transcriptome analysis of 202 newly diagnosed GBM cases and indicated strong associations with genetic mutations such as TP53, EGFR, and NF1 [13]. Gene expression data from three distinct platforms were integrated into one unified data set, and 840 gene signatures were established to classify GBM into the four subtypes. The proneural, neural, classical, and mesenchymal subtypes were characterized by alterations in PDGFRA and point mutations in IDH1, expression of neuronal marker genes, high levels of EGFR amplification, and reduced NF1 expression caused by a localized hemizygous deletion in the region of 17q11.2 containing the NF1 gene, respectively. Although the literature indicates that the proneural subtype is associated with better outcomes and the mesenchymal subtype is associated with poor survival [12-16], there was concern that these findings were influenced by the relatively favorable outcomes of IDH1-mutant GBMs, which are consistently classified as the proneural subtype [17]. TCGA further investigated the correlation between IDH wild-type GBM subtypes and the immune microenvironment by unsupervised clustering and defined three subtypes: the proneural, classical, and mesenchymal subtypes [18]. The neural signature was not enriched in any cluster, and the neural subtype was considered to represent normal cell contamination. This result is consistent with other studies in which the neural subtype was not detected [17, 19].

These approaches have been useful for characterizing the molecular diversity of tumor bulk, namely intertumoral heterogeneity, in GBM patients. However, they have a limited view of intratumoral heterogeneity within individual GBM patients. To analyze intratumoral heterogeneity, Patel et al. used single-cell RNA sequencing (scRNA-seq) to profile 430 cells from five primary IDH wild-type GBMs and found heterogeneous subtype expression in individual cells of single tumors [20]. Darmanis et al. performed scRNA-seq on 3589 cells obtained from the tumor core as well as surrounding peripheral tissue in a cohort of four IDH wild-type GBM patients and observed heterogeneity in intratumor subtypes [21]. More recently, Neftel et al. identified four cell states of IDH wild-type GBM on the basis of extensive gene expression analysis using scRNA-seq: the neural-progenitor-like (NPC-like), oligodendrocyte-progenitor-like (OPC-like), astrocyte-like (AC-like), and mesenchymal-like (MES-like) states. The authors found that most tumors contained all four states. The authors further compared the fraction of cells in each of the four cell states in each tumor with the three TCGA subtypes [18] and found that the AC-like and MES-like meta-modules corresponded to the classical and mesenchymal subtypes, respectively, while the OPC-like and NPC-like meta-modules both corresponded to the proneural subtype [22]. These studies suggest that despite the intratumoral subtype heterogeneity within GBMs, the mesenchymal subtype exists at the single-cell transcriptome level in tumor cells.

The existence of tumor-initiating/propagating or cancer stem–like cells within brain tumors has been identified [23-25], and substantial evidence has confirmed that GBM contains stem cell–like tumor-initiating cells called glioblastoma stem cells (GSCs) [26, 27]. GSCs are defined by the cellular capacity to self-renew, initiate tumors upon serial transplantation, and recapitulate tumor cell heterogeneity [26]. The significance of GSCs has been supported by previous studies showing that GSCs promote resistance to conventional therapies, invasion, angiogenesis, and recurrence [28-32]. Recent studies revealed that GSCs can be classified into two mutually distinct subtypes, the proneural or mesenchymal subtype, on the basis of their gene expression profiles and distinct biological characteristics [33-36]. Recently, Richards et al. used a combination of scRNA-seq and genome-wide CRISPR screening to characterize the cellular phenotypes of GSCs cultured from GBM patients and found that GSCs mapped along a transcriptional gradient between two cellular states: the Developmental and Injury Response states. Developmental GSCs corresponded to the AC-like, OPC-like, and NPC-like cell states, whereas Injury Response GSCs corresponded to the MES-like state [37].

Although various sets of mesenchymal signature genes have been proposed, multiple studies on the mesenchymal phenotype have indicated that GBM patients with the mesenchymal subtype tend to have shorter survival times than patients with other subtypes when the analysis is restricted to samples with low transcriptional heterogeneity [38-40]. The mesenchymal subtype has been characterized as more aggressive,
invasive, angiogenic, inflammatory, hypoxic, necrotic, and multitherapy resistant compared with the other subtypes of GBMs [13, 18, 22, 41-44]. Importantly, the shift of GBM towards the mesenchymal subtype has been identified to be closely associated with treatment-induced phenotypic changes in recurrence. In addition, the mesenchymal transition has been shown to be driven by genetic abnormalities, the tumor microenvironment and immune cells, and altered energy metabolism. The mesenchymal transition of GBMs is described as analogous to epithelial-mesenchymal transition (EMT), which is a reversible cellular program that plays a crucial role in the malignant progression of many types of cancer [12, 45-48]. These findings suggest that understanding the plastic nature of the mesenchymal changes in GBMs is crucial for developing novel therapeutic strategies. Thus, in this review, we will focus on the key factors that affect the course of GBM progression towards the mesenchymal signature.

**Transcription Factors and Gene Mutations in Mesenchymal Transition of GBM**

In an attempt to identify master transcription factors, Carro et al. used reverse-engineering and an unbiased microarray technique to reveal the transcriptional network for the mesenchymal transition of GBMs and found that two transcription factors (C/EBP-β and STAT3) act as the master regulators in the mesenchymal transition [42]. We previously demonstrated that annexin A2 (ANXA2) regulated oncostatin M receptor (OSMR) expression via STAT3 and drove mesenchymal transition in a STAT3-dependent manner in GBMs (the ANXA2–OSMR axis) [49] (Fig. 1 and 2). Furthermore, previous studies showed that STAT3 modulated SLUG expression by directly binding to the Slug promotor, inducing the mesenchymal transformation in GSCs [50, 51]. In line with these results, STAT3 inhibitors such as AZD1480, ruxolitinib, and HJC0512 were shown to abrogate the mesenchymal transition and exhibited antitumor effects in vitro and in vivo [52, 53].

Another important master regulator of the mesenchymal gene expression signature is TAZ. TAZ and its paralog YAP are transcriptional coactivators, and active YAP/TAZ translocate to the nucleus and interact predominantly with TEAD transcription factors to play diverse roles in cancer-relevant functions via the Hippo pathway [54, 55]. Bhat et al. revealed that TAZ in a complex with TEAD2 was directly recruited to the gene promoters that encoded proteins that induce the mesenchymal transition and played an essential role in driving the mesenchymal differentiation of malignant glioblastomas [43].

glioma. Notably, the targets of the mesenchymal network induced by TAZ were relatively nonoverlapping with those driven by STAT3 and C/EBP-β, suggesting that TAZ is an independent modulator of the mesenchymal signatures in GBM [56]. Consistent with this study, Yee et al. found that TAZ was significantly and more highly expressed in the mesenchymal subtype than in other subtypes in TCGA GBM dataset and promoted tumor necrosis [57]. More recently, Uneda et al. identified that the signature genes of differentiated GBM cells (DGCs) were associated with mesenchymal signature genes in the public GBM datasets, and DGCs showed significantly enriched YAP/TAZ/TEAD expression compared with GSCs [58]. Furthermore, Vigneswaran et al. reported that verteporfin, a benzoporphyrin derivative that inhibits YAP/TAZ-TEAD-mediated transcription, induced apoptosis in patient-derived EGFR-amplified/mutant GBM cells and provided significant survival benefit in an orthotopic xenograft GBM model [59].

Intriguingly, NF-κB is closely involved in the complex mesenchymal transcriptional networks. Bhat et al. revealed that TNF-α activated NF-κB, and NF-κB regulated three master transcription factors (STAT3, C/EBP-β, and TAZ) to promote mesenchymal differentiation of GSCs and poor radiation response [41]. Yin et al. indicated that TNF-α-induced NF-κB activation upregulated TGM2 expression and that TGM2 triggered mesenchymal differentiation of GSCs by regulating these three master transcription factors. The authors found that TGM2 induced the proteasomal degradation of GADD153, a negative regulator of C/EBP-β, and thus upregulated C/EBP-β expression [60]. Furthermore, Iwata et al. discovered that TNF-α-induced NF-κB activation increased ICOSLG expression and that ICOSLG expression by mesenchymal GSCs induced IL-10-producing pro-tumorigenic T cells [61]. Regarding the molecular mechanism of NF-κB activation, Kim et al. reported that MLK4, a serine-threonine kinase, was an upstream regulator of NF-κB [62].
Genomic abnormalities in the NF1 gene, such as deletions and mutations, have been reported as one of the major hallmarks of mesenchymal GBMs [13, 14, 18, 22, 63]. NF1 deficiency has been shown to result in increased recruitment of tumor-associated macrophages to tumor sites [18], and NF1 mutation along with the absence of EGFR amplification and PTEN deletion were strongly correlated with tumor-infiltrating lymphocytes in GBM [64]. Marques et al. recently reported that NF1 regulated FOSL1 expression via upregulating RAS/MAPK activity and that FOSL1 played a vital role in the mesenchymal transition, stemness, and tumor growth of GBMs [65].

**Effects of Microenvironment Factors on Mesenchymal Signatures of GBM**

Sottoriva et al. collected four to six tumor fragments from spatially distinct regions within an individual tumor from individual GBM patients to evaluate the regional heterogeneity and identified that each region exhibited the distinct TCGA subtype [66]. Jin et al. later identified that tumor cells in the enhancing region highly expressed proneural signature genes, while those in the necrotic region showed high expression of mesenchymal signature genes [44]. Furthermore, Puchalski et al. described the anatomically-based comprehensive molecular pathology atlas of glioblastoma that assigned individual histological features to genomic alterations and gene expression patterns. This analysis revealed an apparent correlation between anatomical features and molecular subtypes; the mesenchymal signature predominated in the pseudopalisading cells around necrosis and the microvascular proliferation areas, while the proneural signature predominated in the infiltrating tumor and cellular tumor areas [67]. Minata et al. also reported that two distinct types of GSCs exist in the invasive edge and tumor core in GBMs, corresponding to the proneural and mesenchymal subtype, respectively [68]. Indeed, hypoxia is considered a crucial microenvironment factor of the tumor core region of GBMs [11], and GBM cells under the hypoxic and perinecrotic microenvironment showed increased expression of master mesenchymal regulators including C/EBP-β and STAT3 [69]. Furthermore, previous studies demonstrated that the hypoxia-dependent mesenchymal transition was controlled by HIF1α or HIF2α [70-73]. Darmanis et al. found that while macrophages were predominant in the tumor core, microglia were the major population at the invasive edge. This distribution contributed to the shaping of a differential microenvironment, in which anti-inflammatory and pro-angiogenic markers were expressed in the tumor core while inflammatory markers were expressed in the tumor periphery [21]. These results demonstrated that the mesenchymal transition of GBM is closely associated with microenvironmental factors.

The majority of the non-neoplastic infiltrates in the GBM microenvironment is macrophages/microglia [74-79]. Previous studies have shown that glioma-associated macrophages/microglia were enriched in mesenchymal GBMs compared with other subtypes and contributed to the mesenchymal transition [18, 22, 41, 77, 80-83]. Two recent studies using single-cell analysis demonstrated that MARCO, a scavenger receptor expressed on tumor-associated macrophages, drove a phenotypic transition towards the mesenchymal cellular state of GBMs and correlated with poor clinical outcomes [84, 85]. A subpopulation of tumor-associated macrophages characterized by MARCO expression was derived from bone marrow and existed exclusively in IDH wild-type GBMs [84]. Gene set enrichment analysis revealed that the expression of pro-inflammatory gene signatures related to IFN-α response, IFN-γ response, allograft rejection, and TNF-α signaling mediated by NF-κB were attenuated in MARCO-expressing macrophages [84]. Hara et al. recently reported that macrophages induced the MES-like state in GBM by activating STAT3 through the interaction between macrophage-derived OSM and its receptors OSMR/LIFR in complex with GP130. The authors further found that transition into the MES-like state, in turn, increased expression of a mesenchymal program in macrophages and cytotoxicity of T cells [43]. Gangoso et al. revealed that immune attack drove epigenetic changes to reconfigure transcriptional modules in mesenchymal GSCs, conferring an immunosuppressive microenvironment enriched with macrophages and monocytic-myeloid derived suppressor cells in mesenchymal GBMs. The authors proposed a self-reinforcing feedback loop, in which changes in DNA methylation pattern induced by immune attack triggered a myeloid-affiliated transcriptional program in mesenchymal GSCs, resulting in increased recruitment of macrophages, and IFN-γ provided by macrophages in turn promoted epigenetic changes [86]. Dumas et al. found that GBM-initiating cells elicited mTOR signaling in the
microgla but not bone marrow–derived macrophages, and mTOR-dependent regulation of STAT3 and NF-κB activity facilitated a pro-inflammatory tumor microenvironment. The mTOR and tumor-associated microglia signatures were most strikingly correlated in the mesenchymal subtype and not in the proneural subgroup of GBMs [87].

A previous study showed that some IDH wild-type GBMs harbored a substantial T cell infiltration, although not as high as brain metastases [77]. Rutledge et al. demonstrated that tumor-infiltrating lymphocytes were more abundant in the mesenchymal subtype than in other subtypes in GBM and were strongly related to NF1 and RB1 mutations [64]. The differences in the distribution of infiltrating T cell populations (such as cytotoxic T cells, helper T cells, and regulatory T cells) among GBM subtypes have been less conclusive. Kaffes et al. reported that the infiltration of T cell populations of helper T cells, cytotoxic T cells, and regulatory T cells is higher in mesenchymal GBM than in other subtypes [82]. Indeed, some studies demonstrated that CD8+ T cells were mainly associated with mesenchymal types [82]. Indeed, studies reported that the mesenchymal GBM was enriched in CD4+ T cells compared with other subtypes, with no difference in CD8+ T cells [90]. Thus, further studies are required to elucidate the relationship between the infiltrating T cell population and GBM subtypes.

**Effects of Radiotherapy on Mesenchymal Signatures of GBMs**

Although current treatment regimens have prolonged the median overall survival of GBM patients, these treatments are still inadequate in terms of efficacy. Radiotherapy has been a key component of GBM treatment for decades and is used in the Stupp regimen [2]. However, the mesenchymal transition has been considered to contribute to radioresistance [18, 41, 68, 91-94]. Bhat et al. denoted that a subset of proneural GSCs differentiated into the mesenchymal state in a NF-κB-dependent manner, which in turn elicited an increase in CD44-expressing cells and radioresistance [41]. Moreno et al. identified that GPR56, a G-protein-coupled receptor, was enriched in the proneural and classical subtypes of GBMs and lost upon transition to the mesenchymal subtype, and GPR56 inhibited the NF-κB signaling pathway and prevented radioresistance [93]. Furthermore, radiotherapy induced the expression of master mesenchymal regulators such as STAT3 and C/EBP-β and promoted the proneural-to-mesenchymal shift [92]. Goffart et al. found that GSCs residing in the subventricular zone (SVZ) exhibit specific resistance to radiation in vivo, and these cells have enhanced mesenchymal signatures upregulated by CXCL12 in vitro and in the SVZ environment [91]. In addition, Minata et al. reported that GSCs enriched for a CD133+ proneural signature at the tumor edge were converted to GSCs enriched for CD109+ mesenchymal signatures, and CD109 activated the YAP/TAZ pathway contributing to radioresistance [68]. Several preclinical studies have been conducted to overcome radiotherapy resistance and radiotherapy-induced mesenchymal transition. The combination of the STAT3 inhibitor such as AZD1480 and ruxolitinib with radiation attenuated the mesenchymal transition and extended survival in vivo [52]. YM155, a potent survivin suppressant and radiosensitizer, decreased the mesenchymal signatures of GBM cells, enhanced radiosensitivity, and prevented a radiation-induced invasion by targeting STAT3 [95].

**Effects of Chemotherapy on Mesenchymal Signatures of GBM**

Temozolomide (TMZ), a DNA alkylating agent, has been widely used as standard chemotherapy for newly diagnosed GBM since the FDA first approved it in 2005, and the Stupp regimen has become widely used [2]. TMZ induces hypermutation or mutagenesis, and these alterations might contribute to the mesenchymal transition [96, 97]. Herting et al. established high-grade glioma mouse models corresponding to the mesenchymal subtype by NF1 silencing and the proneural subtype by PDGFB overexpression and found that the NF1-deleted mesenchymal model was less sensitive to both radiation therapy and TMZ than the PDGFB-overexpressing neuronal model [98]. Wang et al. established TMZ-resistant glioma cells and showed that they exhibited upregulation of mesenchymal signatures mediated by CDC20 [99]. Other studies showed that transcriptional regulators such as FOXO1 or NF1A played a crucial role in TMZ resistance and the mesenchymal transition of GBM cells [100, 101].

Because angiogenesis is one of the hallmarks of GBMs, anti-angiogenic therapies such as bevacizumab, an anti-VEGF monoclonal antibody, were expected to have therapeutic effects. However, phase III studies (AVAglio and RTOG-0825) showed no survival benefit.
of bevacizumab for newly diagnosed GBM [5,6]. One possible reason for this insufficient therapeutic effect may be the mesenchymal transition induced by bevacizumab. Piao et al. performed gene expression profiling and identified that genes associated with mesenchymal signatures were increased in GBM cells after VEGF treatment compared with untreated controls [102,103]. Other studies revealed that bevacizumab treatment accentuated the mesenchymal transition and conferred resistance to bevacizumab through Wnt/β-catenin signaling, MET activity in a hypoxia-independent manner, ZEB1 expression that altered the metabolic state of bevacizumab-resistant cells via GLUT3 activity, and bevacizumab-induced macroautophagy/autophagy in GSCs [104-108]. Furthermore, a retrospective analysis of the AVAglio trial demonstrated that bevacizumab in combination with standard therapy prolonged PFS over placebo in GBM patients with the mesenchymal and proneural subtype, but prolonged OS was only observed in patients with the proneural subtype [109].

Effects of Recurrence on Mesenchymal Signatures of GBM

Patients with GBM have a poor prognosis as tumor recurrence is inevitable with the current standard of care, and recurrent tumors often have a more aggressive phenotype. [110]. There is currently no standard treatment for patients with recurrent GBM. Numerous regimens, including immunotherapy, antiangiogenic therapy, molecular targeted therapy, reirradiation, stereotactic radiosurgery, and combination therapy, have been investigated in clinical trials [111-113]. However, the prognosis for patients with recurrent GBM remains poor. Thus, elucidating the properties of GBMs at recurrence is crucial for better understanding of the evolution of tumors and improving the treatment of GBMs [114]. Mesenchymal GBMs at tumor recurrence were found to have trends toward a worse overall survival, and reduced expression of mesenchymal signature genes was correlated with more favorable survival and longer time to recurrence in GBM patients [115,116]. Importantly, recurrent GBMs frequently shifted toward the mesenchymal subtype, which was characterized by the loss of OLIG2 expression and the upregulation of YKL40, CD44, STAT3, and VIM expression [12,117]. Furthermore, elevated transcriptional heterogeneity was associated with a higher subtype switching at tumor recurrence, and recurrent GBMs, especially those that underwent the mesenchymal transition, were associated with a higher enrichment of tumor-associated macrophages [18,118]. EGFR amplification or EGFRvIII mutation is a characteristic of the classical subtype of GBM [13,18,116]. Interestingly, van den Bent et al. showed that the EGFR amplification status and EGFRvIII expression remained stable in the majority of GBMs evaluated. However, when focusing on EGFRvIII-expressing tumors, approximately half of them lost EGFRvIII expression at recurrence [119]. Cioca et al. reported that both primary and recurrent GBMs displayed EGFR expression; approximately 42% of recurrent tumors had reduced EGFR expression compared with primary tumors, and 54% had comparable expression in their cohort [120]. Another study demonstrated that loss of EGFRvIII expression in recurrent tumors was prominently associated with a shift from the classical subtype to other subtypes [116].

Longitudinal transcriptional analysis conducted by TCGA revealed that 45% of IDH wild-type GBMs switched subtype upon recurrence [18]. Other studies showed that approximately 30-67% of primary GBMs underwent subtype changes at recurrence [13,116]. The mesenchymal subtype has been considered as the most stable subtype with 45-55% retaining the same subtype at recurrence. However, it is important to note that the frequency of the transition to the mesenchymal subtype was not significant upon tumor recurrence and some tumors shifted to the proneural subtype and others to the classical subtype at recurrence [18,116]. More research is needed to elucidate the molecular biological mechanisms that predispose to the shift toward the mesenchymal subtype upon recurrence.

Effects of the ANXA2–STAT3–OSMR Axis on Mesenchymal Transition of GBM

We previously established two glioma cell lines, J3T-1 and J3T-2, that exhibit distinct invasion patterns and molecular expression and have examined the molecular and pathological phenotypic shifts of GBMs [49,121-124]. We showed that the ANXA2–STAT3–OSMR axis drove the pathological aggressiveness and mesenchymal transition of GBMs [49] (Fig.3). Consistent with our findings, several studies have reported that ANXA2 promoted tumor aggressiveness and mesenchymal transition in GBMs [125-132]. OSMR and its ligand OSM have been reported to
induce tumorigenesis, tumor aggressiveness, mesenchymal transition, radiotherapy and chemotherapy resistance, shaping an immunosuppressive microenvironment in GBMs [43,133-140]. Notably, OSM is produced by macrophages in the GBM microenvironment and elicited the mesenchymal state in GBM cells via the interaction with its receptors OSMR and LIFR [43,137]. Given that ANXA2 has been reported to exert an effect on macrophage migration to the tumor site and activation [141-145], the ANXA2–STAT3–OSMR axis might drive macrophages to the tumor site and contribute to the development of a tumor ecosystem distinct to GBM. The humanized anti-OSM monoclonal antibody GSK2330811 has recently been validated in a phase II clinical trial to treat diffuse cutaneous systemic sclerosis (NCT03041025), and GSK2330811 exhibited anti-tumor effects in cervical squamous cell carcinoma in vivo [146]. Whether GSK2330811 is a new therapeutic approach for GBM by inhibiting the ANXA2–STAT3–OSMR axis should be investigated.

**Conclusions and Future Perspectives**

In this review, we have discussed the molecular mechanisms related to the mesenchymal transition of GBMs and the clinical significance. There have been significant developments in our understanding of the inter- and intratumoral heterogeneity of GBMs and the interactions with the microenvironment. However, these insights have not yet yielded significant improvements in patient outcomes. One issue is that there is currently no way to know the properties of an individual tumor prior to surgery, making it difficult to promptly tailor treatment strategies on the basis of the characteristics of the tumor. With the development of computational algorithms, artificial intelligence methods are well poised to improve the accuracy of diagnosis and clinical decisions [147]. In particular, machine learning and deep learning methods are being applied to radiomics and radiogenomics. The term radiomics refers to the process of converting images into mineable data and analyzing the data to support decision making, and radiogenomics refers to the process of integrating radiological data with genome-scale data [148,149]. These radiomics and radiogenomics tools have the potential to capture spatial and molecular heterogeneity through non-invasive sampling and to stratify patients into more precise initial diagnostic and therapeutic procedures. In the field of neuro-oncology, radiomics and radiogenomics can predict tumor grade and genetic status including IDH mutation and 1p19q-codeletion.

![Fig. 3 Schematic diagram of the ANXA2-STAT3-OSMR axis. We previously demonstrated that ANXA2 regulates OSMR expression through STAT3 phosphorylation in GBMs and that this ANXA2-STAT3-OSMR axis drives mesenchymal transition, cell proliferation, invasion, and angiogenesis [49].](image_url)
status in glioma to clinically useful accuracies [150-157]. Given these advances, the classification of the molecular subtypes of GBM based on imaging alone may soon become a possibility. Comprehensive efforts to further unravel the inter- and intratumoral heterogeneity of GBM and translate these insights into clinical decisions will ultimately contribute to improved patient outcomes.

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