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TOPIC REVIEW

# Glioblastoma and acute myeloid leukemia: malignancies with striking similarities

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**Abstract**
Acute myeloid leukemia (AML) and glioblastoma (GB) are two malignancies associated with high incidence of treatment refractoriness and generally, uniformly poor survival outcomes. While the former is a hematologic (i.e. a "liquid") malignancy and the latter a solid tumor, the two diseases share both clinical and biochemical characteristics. Both diseases exist predominantly in primary (de novo) forms, with only a small subset of each progressing from precursor disease states like the myelodysplastic syndromes or diffuse glioma. More importantly, the primary and secondary forms of each disease are characterized by common sets of mutations and gene expression abnormalities. The primary versions of AML and GB are characterized by aberrant RAS pathway, matrix metalloproteinase 9, and Bcl-2 expression, and their secondary counterparts share abnormalities in TP53, isocitrate dehydrogenase, ATRX, inhibitor of apoptosis proteins, and survivin that both influence the course of the diseases themselves and their progression from precursor disease. An understanding of these shared features is important, as it can be used to guide both the research about and treatment of each.

**Keywords** Acute myeloid leukemia · Glioblastoma · GBM · AML · Cancer genetics

## Introduction

Acute myeloid leukemia (AML), a hematologic malignancy characterized by the accumulation of immature myeloid cells, and glioblastoma (GBM), a WHO grade IV neoplasm of immature glial cells, are both potentially devastating diagnoses that share several characteristics that can collectively inform their clinical management. AML is one of the most common hematologic malignancies in adults [106], while GBM is the most common primary brain tumor [102]. Both are associated with poor survival in most subtypes: the 5-year survival rate for AML is 28% for patients under 40 [79] and less than 10% for older patients [36], and the 2-year survival rate for patients receiving the standard-of-care therapy for GBM (radiotherapy plus temozolomide followed by adjuvant temozolomide) is 26.5% [102]. In this review, we delineate several important similarities between AML and GBM including evolution from precursor lesions, outcomes, and shared molecular pathways. An understanding of the similarities between these two families of cancer may open up new avenues of therapy for both.

### Progression from precursor disease

AML and GBM have primary and secondary forms. Secondary AML can arise from antecedent hematological disorders, including myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), aplastic anemia, and myeloproliferative neoplasm (MPN)(which includes essential thrombocythemia, polycythemia vera, and primary myelofibrosis) [79]. Secondary GBM may arise from low-grade astrocytoma and oligodendroglioma [22].

Only a small fraction of AML and GBM is secondary, occurring in 10–20% [116] and < 5% of cases, respectively [72]. MDS and MPN have a lower propensity to undergo malignant transformation than low-grade glioma. Approximately 30–40% of MDS transforms to AML [4], while

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essential thrombocythemia, polycythemia vera, and primary myelofibrosis have 10-year malignant transformation rates of 1, 4, and 20%, respectively [85]. Conversely, Jaeckle et al. [41] found that 40% of oligodendrogliomas, 70% of oligoastrocytomas, and 74% of low-grade astrocytomas progressed to high-grade tumors.

In general, secondary AML and GBM are associated with worse survival compared to their primary counterparts, but for different reasons. The secondary presentation of AML is not necessarily an independent predictor of adverse outcomes, but the increased median age at presentation suggests that patients are more likely to have other physical or genetic comorbidities that may complicate management [116]. Patients with secondary GBM have shorter survival than those with primary GBM, although the former is more common in younger patients [60]. Thus, this finding is likely due to factors independent of age.

## Pertinent genetic pathways to secondary disease

The development of AML and GBM from more indolent precursor lesions is associated with dysfunction in multiple molecular pathways. Determining the common pathways and the extent of their involvement in the pathogenesis of both diseases can aid in management and in the development of therapeutic targets. Recent efforts using TCGA data have revealed that GBM [110] and AML [71] share many mutations in common, including in TP53 and IDH1/2. Several of the molecular pathways discussed below are important not just to the development and progression of precursor disease states but also to AML and GBM themselves.

### TP53

Expression of TP53, a key tumor suppressor, is frequently altered in both AML and GBM and their precursors. TP53 abnormalities are less common in MDS (5–20%) [104] and MPN [84] than in diffuse astrocytoma (60–80%) [65] and anaplastic astrocytoma (82%) [50] but have a clearer role in malignant transformation to AML. The rate of leukemic transformation in MDS with TP53 mutation can range from 50% [40] to 92% [56] compared to 15.5% [40] to 25% [56] in MDS with wild-type TP53. TP53 mutations are also implicated in the leukemic transformation of MPN [19, 109] and may synergize with JAK2 mutations to accelerate this process [84]. Conversely, while low-grade gliomas with TP53 mutation transform to GBM more quickly than those with wild-type TP53 [91], secondary GBMs have similar rates of TP53 mutation to lower-grade astrocytomas, which suggests that these low-grade lesions are merely checkpoints on the path to a substantially more dangerous tumor [65].

While TP53 mutations may play different roles in the development of secondary AML and GBM, TP53 mutations are considered adverse prognostic factors in AML and are associated with worse survival [44, 66]. TP53 mutations have been shown to correlate with shorter survival and decreased response to temozolomide in GBM [112]. Knockdown of mutant TP53 has been shown to increase temozolomide sensitivity in GBM [112], and knockdown of inhibitors of wild-type TP53 has been shown to synergize with XIAP inhibition in AML cell lines to accelerate apoptosis [14], thus demonstrating a target for chemotherapy in both diseases. To this end, a phase II clinical trial evaluating the safety and efficacy of SGT-53 (an intravenous, tumor-targeted, liposomal p53 delivery system) in conjunction with temozolomide in patients with recurrent GBM is currently underway [81]. Given that the correction of TP53 abnormalities has been demonstrated to enhance chemotherapy response in both GBM and AML, the results of this trial could profoundly impact the treatment of both diseases.

### Isocitrate dehydrogenase 1 and 2

Isocitrate dehydrogenase 1 and 2 (IDH 1 and 2) are components of the citric acid cycle. Mutations of IDH1/2 give rise to high levels of 2-hydroxyglutarate (2-HG), which has been described as an oncometabolite [86]. As is the case for TP53, IDH 1/2 mutations are less common in AML precursors (5%) [10] than in diffuse and anaplastic astrocytoma (> 80%) [73]. IDH mutations have different effects on malignant transformation in AML and GBM precursors. IDH1-mutant MDS cases have a malignant transformation rate of 50%, compared to 18% in controls [77]. Conversely, IDH1/2 mutations appear to be associated with neither rate of nor time to malignant transformation in low-grade glioma [74].

Similarly, IDH1/2 mutations have different prognostic roles in AML and GBM. IDH1/2 mutations alone do not appear to correlate with worse response to treatment, overall survival, or relapse-free survival in AML [26], while mutations in IDH1/2 correlate with improved overall survival, progression-free survival, and responses to temozolomide and surgical resection in secondary GBM [24, 49].

The IDH pathway is an example of how treatment of AML or GBM can influence thinking about treatment paradigms of the other. Clinical trials of IDH inhibitors have recently begun in both AML and glioma, with agents like AG-120 and AG-221 receiving fast-track and orphan drug approval from the FDA [1]. Trials of small-molecule mutant IDH inhibitors have demonstrated efficacy in reducing intracellular 2-HG levels in xenografted glioma cell lines [25]. In a trial of IDH2 inhibitor AG-221 (Enasidenib), a complete remission rate of 28.5% was observed in patients with relapsed or refractory AML. Stable disease, a previously rare treatment outcome in AML, was achieved in an additional 43% [1]. Stein et al. [96] observed complete remission in 19.3% and an overall response rate of 40.3% in patients with

relapsed or refractory AML treated with Enasidenib, with stable disease observed in 48.3%. A combined phase I and II trial of AG-221 in glioma patients has been completed [99]. A phase I trial of IDH305, an IDH inhibitor targeting the R132 mutation, in relapsed or refractory AML demonstrated an overall response rate of 33% with minimal toxicity [9]. Because of the novelty of these agents, more time is needed to evaluate their effects on survival outcomes [95]. A phase II trial of IDH305 for grade II and III glioma is scheduled to begin in 2018 [107]. AG-881, an IDH1/2 inhibitor, is currently in phase I trials in patients with AML [100] and glioma [101]. Phase I trials of IDH1 peptide vaccines are currently being conducted for grade II glioma [39] and for grade III and IV glioma [80]. These vaccines have not been tested in AML but could prove to be useful given the results of other methods of IDH inhibition.

#### ATRX

ATRX is a protein involved in telomere maintenance and epigenetic regulation of gene expression [37, 43]. Germline mutations in this protein are associated with alpha thalassemia and severe mental retardation [93]. In contrast to TP53 and IDH, ATRX mutations appear to be much more common in GBM [36] and do not seem to have a major role in the development of secondary AML [32]. ATRX mutations are found in 71% of grade II and III astrocytomas, and nearly all of these (99%) have IDH1/2 mutations [43]. Because of the favorable prognostic value of IDH1/2 mutations in some studies discussed above, it is unsurprising that ATRX loss is associated with better progression-free survival in low-grade glioma [13].

While acquired alpha thalassemia has been demonstrated in AML and MDS [92, 94], ATRX mutations are not likely involved in the development of these malignancies per se. While ATRX mutations occur in 43% in MDS associated with unexplained microcytosis, the estimated overall prevalence is between 0.2 and 0.8% [37]. Additionally, the prevalence of MDS and other hematologic malignancies is not higher in patients with germline ATRX mutations [93]. Steensma et al. [92] found that, in 17 cases of leukemic transformation of MDS, only one patient retained an alpha thalassemic phenotype. The role of ATRX in these hematologic cancers is thus less likely causative and simply definitive of a substantially more severe subtype.

#### Inhibitor of apoptosis proteins and Smac mimetics

Inhibitor of apoptosis proteins (IAPs) are expressed at high levels in many human malignancies, including both AML [16, 97] and GBM [105]. IAPs inhibit caspases and suppress apoptosis and thus are promising therapeutic targets [90]. IAPs have a clearer role in the malignant transformation of low-grade glioma than in that of AML precursors. BIRC3 overexpression has been associated with decreased median survival in low-grade glioma patients [35]. The role of IAPs in the malignant transformation of MDS and MPN is unknown, although in one study it was noted that expression of several IAPs in MDS cells peaked just before leukemic transformation [114].

Because of this, Smac mimetics, a novel class of drug that inhibits IAPs, have been the subject of recent clinical investigation. These agents have been studied in clinical trials as both single agents and in combination [5, 31]. The Smac mimetic birinapant reduces intracellular levels of several members of the IAP family, especially cIAP1 and induced apoptosis in AML cell lines—including blasts and stem cells—without substantial toxicity to normal bone marrow [16]. Recently, the efficacy of LCL161, an oral Smac mimetic, in patients with myelofibrosis with intermediate to high IPSS risk and refractory to 2 or more therapies was demonstrated a 33% overall response rate [78]. A combination of Smac mimetic BV6 and temozolomide has been shown to reduce viability and promote apoptosis in several GBM cell lines [111], though it has also been suggested that BV6 could facilitate tissue invasion [62].

#### Survivin

Survivin is an IAP family member and a key mediator of mitotic progression, angiogenesis, and chemoresistance [17, 23], and, unlike the other IAPs, has a clearer role in the progression of low-grade glioma than in that of AML precursors. Survivin expression is increased in MDS [33] and MPN [64] relative to healthy controls and again peaks before malignant transformation but is not associated with survival [33]. Conversely, survivin expression is associated with faster progression of low-grade glioma to GBM [113] and diminished survival [20].

In spite of this difference, survivin offers a potential therapeutic target in both AML and GBM, as its expression in normal tissue is rare outside of fetal development [20]. Oligonucleotide inhibition of survivin has been shown by several authors to reduce cell viability and promote apoptosis in some AML cell lines [18, 42, 47] and, in combination with temozolomide, in GBM cell lines [23].

### Pertinent pathways to primary disease

While the development of secondary AML and GBM is associated with dysregulation in several shared pathways, the emergence of their primary counterparts is also characterized by a unique fingerprint of aberrant gene expression.

### RAS pathway

Ras is a G-binding protein whose activation is a common feature of human malignancies and whose downstream effectors like Raf, MAPK, PI3K, and Ral-guanine are involved in cell cycle progression and cell survival [22]. RAS mutations are found in approximately 20% of AML [4, 67] and are rarely found in GBM [22], but upstream mutations in this pathway are common in both primary diseases. Epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its associated receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR), upstream components of the Ras pathway, are frequently over-activated or mutated in GBM [48, 49, 72]. Elevated VEGF expression, VEGFR mutation [45], and EGFR mutation [103] have also been observed in AML.

Oddly, the potential utility of upstream RAS pathway inhibitors seems to exist for AML and not GBM. Trials of EGFR, VEGFR, and PDGFR blockers as monotherapies have failed in GBM [58]. Sorafenib, a VEGF antagonist, has been shown to induce complete remission [3] and longer overall and progression-free survival [11] in post-HCT FLT3-ITD AML. Sorafenib [87] and VEGF inhibitor bevacizumab [63] have had no effect on survival in GBM and have instead been shown to induce treatment resistance [63, 87].

### Matrix metalloproteinase 9 (MMP-9)

MMP-9 is part of a large family of matrix metalloproteinases that are active in various physiologic processes like tissue remodeling. However, the ability of these enzymes to digest the extra cellular matrix also makes them highly important to the invasiveness of several cancers [115]. MMP-9 expression is found in 69% of primary GBM and 14% of secondary GBM [72] but not in normal brain tissue [21]. It has been found to be constitutively active in the bone marrow morphonuclear cells of both healthy controls and AML and MDS patients [88], although its relative prevalence in primary AML is unclear. In spite of similar expression profiles between diseases, MMP-9 appears to influence GBM only through an association with shorter overall and progression-free survival [115]; MMP-9 is associated with remission but not survival in AML [61].

### BCL-2

Bcl-2 is part of a family of proteins that governs cell cycle entry and apoptosis and functions as an oncogene [68]. Bcl-2 expression abnormalities are found in 60–61% of primary GBM [55] and in nearly half of primary AML [57]. Not only does aberrant Bcl-2 expression exhibit preponderance in both primary processes, but it also appears to negatively influence survival. Bcl-2 expression has been independently associated with decreased treatment response and survival in AML [46] and with tumor grade in glioma and chemoradiotherapy resistance in GBM [83].

Bcl-2 is showing promise as a therapeutic target in both diseases. A trial of venetoclax, an oral Bcl-2 inhibitor, demonstrated better overall response rates in AML (19%) than with any other monotherapy [54], and trials of Bcl-2 inhibitors obatoclax [7] and navitoclax [75] have demonstrated their ability to sensitize GBM cells to apoptosis in vitro. Furthermore, a historically rare hematologic neoplasm that was previously classified in AML and related family of neoplasms category, blastic plasmacytoid dendritic cell neoplasm (BPDCN), was recently demonstrated to have sensitivity to BCL-2 inhibition via venetoclax (in both in vitro and in vivo settings) [69].

A summary of the various pathways that have been targeted in both AML and GBM can be found in Table 1. While this list is not exhaustive, it is important to note the similarities in the pathways targeted in each disease and the agents used to do so.

## Subtypes of disease

AML and GBM are each classified into several subtypes [38, 110]. AML occurs in M0–M7 varieties according to the FAB classification system, with M0–M5 originating from leukocyte precursors, M6 from immature erythrocytes, and M7 from immature megakaryocytes [38]. GBM is roughly classified into proneural, neural, classical, and mesenchymal subtypes [51, 110]. An important difference between the two diseases arises here in that AML may be classified based on morphology alone [89], while extensive cytogenetic analysis using The Cancer Genome Atlas (TCGA) data has been used to classify GBM [110]. Proneural and classical GBM are most significant to the present review. The former is associated with TP53 and IDH1/2 mutation, while the latter is associated with EGFR mutation and a relative absence of TP53 mutation [110].

**Table 1** Targeted therapy options for AML and GBM

| Pathway | AML | GBM |
|---|---|---|
| TP53 | – | SGT-53 |
| IDH1/2 | AG-221, IDH305, AG-881 | AG-221, IDH305, AG-881, IDH peptide vaccines |
| IAP/Smac | LCL161 | BV6 |
| Survivin | Oliogonucleotide inhibition | Oliogonucleotide inhibition |
| RAS | Sorafenib | Sorafenib, bevacizumab |
| Bcl-2 | Venetoclax | Obatoclax, navitoclax |

## Discussion

The practical use of the information discussed here hinges not just on what features these diseases have in common but also the extent to which they have them in common. While alterations in many of the pathways discussed above very clearly contribute more to primary than secondary disease, or vice-versa, they may occur more frequently in GBM or AML. Thus, GBM cannot be treated as a purely solid or purely liquid tumor.

AML and GBM can be difficult to treat, and prognoses for each remain dismal overall. Importantly, there are subsets of these malignancies that evolve from more indolent precursors. Maintaining tumors in these more benign states may be a therapeutic strategy. However, early detection and monitoring is difficult for AML and GBM given the relative absence of precursor lesions.

Several other solid tumor types can emerge from precursor lesions. Colorectal cancer, lung adenocarcinoma, and melanoma emerge from colonic polyps [12], atypical adenomatous hyperplasia [53], and dysplastic nevi [34, 108], respectively. What sets these tumors apart from AML and GBM is the fact that most cases of each of these tumors are secondary [12, 34, 53, 108], while secondary AML and GBM represent a small minority of cases. These solid tumors certainly do not constitute a comprehensive list of solid tumors. However, it is important to note that, when compared to other secondary solid tumors, GBM behaves more like AML in that the vast majority of cases tend to be primary.

GBM is more like AML than other solid tumors in that solid tumor precursors are not typically associated with any significant morbidity or mortality in and of themselves. In an 8-year prospective study of patients with colonic polyps, Stoian et al. [98] observed a 0% mortality rate in patients with polyps that did not undergo malignant transformation. Barrett's esophagus, a metaplastic precursor to esophageal adenocarcinoma, is considered to be asymptomatic [76], as is AAH [76]. Dysplastic nevi are considered to be insignificant outside of their potential for malignant transformation [28]. Once these precursors have progressed to malignancy, the dissimilarity of GBM to other solid tumors is accentuated by the fact that GBM inevitably recurs even after aggressive resection and chemotherapy [58], while surgery may achieve cure in other—even very aggressive—solid tumors, including those of the esophagus [27] skin [29], lung [72], and pancreas [6].

The treatment of GBM is complicated by intra-tumor genetic heterogeneity and even more so by the fact that treatment can drive this phenomenon [82].Therefore, many of the molecular pathways discussed below may not be equally altered in adjacent regions of a tumor, which makes targeted chemotherapy a difficult prospect. Malignant cell populations in AML are equally diverse. Several different sub-populations exist, each with its own unique genetic and epigenetic profile. As with GBM, these cell populations may be differentially susceptible to certain therapies, which may partially account for the poor outcomes seen in AML [60]. Other solid tumors, such as those of the colon and breast, also demonstrate considerable intra-tumor genetic and epigenetic heterogeneity that can contribute to treatment resistance and relapse [8]. Intercellular interactions add an additional aspect of complexity to cell populations in both GBM [70] and AML [15] and can contribute to treatment resistance in both diseases.

In spite of within-disease genetic variation in secondary GBM and AML, abnormalities in several of the same genetic pathways are associated with their development from precursor states and prognosis. TP53 mutations, found more commonly in both secondary GBM and AML, is associated with faster malignant transformation and shorter survival; accordingly, therapies aimed at mitigating irregular activity in this pathway have shown promise in both diseases. It is important to note that TP53 pathway aberrations are not unique to GBM and AML. TP53 mutations are found in a majority of ovarian, bladder, lung, esophageal, and pancreatic cancers and are common occurrences in several other types [59].

IAPs are implicated in the development of secondary AML and GBM. The roles of these molecules are better understood in the context of the malignant transformation of low-grade to higher-grade glioma than they are for that of MDS or MPN, but therapies directed against these pathways have shown promise in early investigations mainly by acting synergistically with existing drugs to reduce malignant cell viability. Like TP53 mutations, abnormalities in IAP expression are found in many other cancers, like those of the pancreas, esophagus, breast, kidney, and skin [32].

IDH1/2 mutations are also common features of secondary GBM and AML. IDH mutations are not only common in AML and GBM but also more common in these than in any other cancer save for chondrosarcoma and cholangiosarcoma [10, 30]. While GBM is like AML in that they frequently share this mutation, AML is unique in that IDH mutations can have negative prognostic value, whereas IDH mutations carry positive prognostic value in GBM and cholangiosarcoma [52]. In some cancers, IDH status has no prognostic value. For example, Amary et al. [2] found no survival difference in chondrosarcoma between patients with and without IDH mutations. The frequent concurrence of ATRX mutations and IDH mutations in glioma may result in tumors that are far less lethal than those with wild-type copies of each.

Primary AML and GBM also share several genetic abnormalities not commonly found in their secondary counterparts. RAS and MMP-9 are commonly aberrantly expressed in both. However, unlike the genetic abnormalities found in secondary AML and GBM, they are not consistently associated with differing survival outcomes (aside from MMP-9 in GBM and Bcl-2 in both diseases). Additionally, these proteins seem to offer little in the way of therapeutic targets or prediction of responses to existing treatments save for RAS and MMP-9 in AML and Bcl-2 in both diseases.

## Conclusion

AML and GBM have much in common, particularly in their secondary progression from precursor diseases, which, in both cases, are themselves are a cause of great morbidity and mortality. The development of secondary AML and GBM hinges on abnormalities in several common genetic pathways. Many of these are the targets of new therapeutic agents. Primary AML and GBM also share many genetic irregularities that, while also found in other cancers, largely do not appear to influence outcome and thus generally do not appear to make useful therapeutic targets—though exceptions exist. There are subpopulations of patients with AML or GBM that display improved survival and treatment response, though the basis for this variation differs between the two diseases. Thus, while AML and GBM have both clinical and genetic features in common, their common clinical characteristics set them apart from other solid tumors.

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### Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest to disclose with regards to this manuscript.

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