

# Insights into Molecular Mediators of Oxidative Stress and Inflammation in Glioblastoma Multiforme

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## ABSTRACT

Glioblastoma multiforme (GBM) is one of the most common aggressive and fatal forms of adult brain tumors. According to WHO classification, GBM is usually classified as a grade IV form of a brain tumor. Glioblastoma multiforme exhibits high intra- and inter-tumoral heterogeneity. Free radical generation in GBM plays a robust role in promoting and inducing inflammatory processes mediated by various signaling pathways mainly focusing on Janus-kinases (JAK). Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) stimulates signal transducer activating transcription factor 3 (STAT3) and JNK to induce proinflammatory cytokines, such as, interleukin (IL)-2, IL-6, and IL-8 to aggravate the inflammatory process. This review summarizes the convergence of inflammation and oxidative stress and examines the potential therapeutic targets aimed at the molecular markers in GBM.

**Keywords:** Glioblastoma multiforme, Inflammation, Molecular markers, Oxidative stress.

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## INTRODUCTION

Glioblastoma multiforme (GBM) is considered to be the most aggressive tumor form of the central nervous system (CNS), with extensive invasion and differentiation.<sup>1</sup> Though GBM is a rare disease with a global incidence of less than 10 per 100,000 people, its poor prognosis with a survival rate of 14–15 months after diagnosis makes it clinically challenging.<sup>2</sup> The difficulty in GBM treatment is usually attributed to several clinical hurdles, such as, failure of drug delivery through the blood–brain barrier, tumor unresponsive to chemotherapy, and development of multidrug resistance by tumor cells.<sup>3</sup>

Several physiological processes which include inflammation, apoptosis, oxidant/antioxidant balance, differentiation, and angiogenesis contribute to GBM.<sup>4</sup> Oxidative stress is one of the major contributors to the pathogenesis of GBM; wherein it triggers lipid peroxidation of cellular membranes, oxidation of proteins, and DNA damage, leading to changes in chromosome structure, genetic mutation, and/or modulation of cell growth.<sup>5</sup> Many reports suggest that intracellular accumulation of reactive oxygen species (ROS) in the mammalian brain is directly responsible for cellular and tissue dysfunction.<sup>6</sup> Excess free radicals generated induce oxidative stress and develop extensive DNA damage, thereby making it a major contributor to GBM development.<sup>7</sup>

Genetic and molecular alterations through multi-step tumorigenesis lead to the development of primary and secondary high-grade glioma, based on clinical, molecular, and pathological characteristics.<sup>8</sup> Primary GBM involves loss of heterozygosity (LOH) of chromosome 10 bearing phosphatase homolog (PTEN), gene amplification of epidermal growth factor receptor (EGFR), or deletion mutation of EGFR to EGFRvIII and enhanced activity of telomerase reverse transcriptase (TERT). While, secondary GBMs result from mutations in chromosome 19q-LOH holding isocitrate dehydrogenase (IDH1/2), loss of function in the tumor suppressor protein 53 (TP53),  $\alpha$ -thalassemia/mental retardation syndrome X-linked ATRX, platelet-derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ ).<sup>9</sup> Most of these alterations are reflected at the cellular

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level mediated, mostly by receptor tyrosine kinase/RAS/mitogen-activated protein kinase (MAPK)/phosphatidylinositol-3-kinase (PI3K) signaling pathway.<sup>10</sup>

Heterogeneity in GBM can be attributed mainly due to: (i) aberrations at genetic and transcriptional level and (ii) molecular markers.<sup>11</sup>

## ABERRATIONS AT GENETIC AND TRANSCRIPTIONAL LEVEL AND MOLECULAR MARKERS

Gain- or loss-of-function in proto-oncogenes and tumor-suppressor genes has been associated with tumor heterogeneity, including drug resistance. Epidermal growth factor receptor, a transmembrane tyrosine kinase, functions as a critical player involved in proliferation, migration, and cell survival in most cancers.<sup>12</sup> Almost in 40–60% of GBM, amplification of EGFR or deletion, mutation of EGFR to EGFRvIII, a truncated protein is formed, resulting in mitogenic signals. Recent research has reported that inhibitors targeting receptor tyrosine kinases have shown to exhibit promising treatment strategy for GBM; however, failures of treatment have been observed in clinical trials.<sup>13</sup>

Another important hallmark feature of GBM is a mutation in IDH. Isocitrate dehydrogenase is an important enzyme that catalyzes the conversion of isocitrate in the presence of NAD<sup>+</sup> to form carbon dioxide and  $\alpha$ -ketoglutarate in Krebs's cycle.<sup>14</sup> This results in the formation of oncometabolite, 2-hydroxyglutarate which disturbs DNA methylation, gene transcription, and histone alterations; moreover, mutations may decrease NADPH formation, promoting oxidative stress and leading to DNA damage.<sup>14</sup> Isocitrate dehydrogenase mutations have been reported in more than 80% of cases of secondary GBM. According to WHO 2016 criteria, the distorted translocation of the whole chromosome arm 1p19q co-deletion along with IDH mutation has been classified as oligodendroglial phenotype.<sup>15</sup> Therapies targeting these mutations showed a favorable increase in the survival rate of patients and well responsiveness toward temozolomide (TMZ) and radiotherapy.<sup>16</sup>

Recent research in glioma biology has been focused on *ATRX* gene mutation. *ATRX* protein is involved in genomic stability, chromatin remodeling, and DNA methylation. It is responsible for maintaining telomere length which controls cell survival and proliferation. Furthermore, it was observed that *ATRX* mutation is associated with IDH mutations.<sup>17</sup> Another study by Amorim et al. has reported anaplastic gliomas with *ATRX* loss and IDH subsets cause exposure to more treatment failure.<sup>18</sup>

Another aberration in GBM mainly focuses on TERT enzyme.<sup>19</sup> It is a ribonucleoprotein involved in the regulation of chromosomal length by the addition of nucleotides using reverse transcriptase. In 85% of grade IV astrocytomas and grade II/III oligodendrogliomas, mutations in the TERT promoter have been reported.<sup>20</sup> Furthermore, there exists a strong correlation between TERT mutations with 1p19q co-deletion, but not with IDH mutations or *ATRX* loss.<sup>21</sup> Studies have reported that gliomas bestow better outcomes with targeted therapies on TERT mutant/co-deleted 1p19q rather than TERT mutant/IDH mutation and without 1p19q co-deletion.<sup>22</sup>

In the past few decades, epigenetic mechanisms of resistance in GBM have been attributed to the methylation status of O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter.<sup>23</sup> O<sup>6</sup>-methylguanine-DNA methyltransferase has served as an important therapeutic target for GBM.<sup>23</sup> TMZ, a standard drug for GBM, induces methylation of MGMT promoter, causes upregulation of tumor suppressor genes, and deduces tumor growth and proliferation.<sup>24</sup> Woo et al. reported that the expression of MGMT methylation status is induced on TMZ-treated xenograft models of GBM and can serve as a predictor of TMZ responsiveness.

A different novel molecule involved in GBM is sodium-independent cystine–glutamate antiporter that is chloride dependent (SLC7A11 or system Xc–xCT), regulated by a nuclear factor (erythroid-derived)-like 2 (Nrf2), a transcription factor involved to balance oxidative stress and controls most of the cellular and physiological functions. xCT with CD98 forms a glutamate–cystine antiporter system that exchanges cystine in place of glutamate in the cell.<sup>25</sup> Cystine gets reduced to cysteine, a rate-limiting amino acid in the production of cellular glutathione (GSH). xCT has critical roles in antioxidant defense responses, primarily in the primary brain tumors.<sup>26</sup> Furthermore, studies revealed xCT associated with glioma-induced neuronal cell death, perifocal edema, and tumor-associated epileptic events. Another study by McBean has also suggested the closer association of cysteine and GSH involved in the balance of intracellular/extracellular redox

balance along with neuronal protection. Deregulation in this transporter system can lead to neurological disorders.<sup>26</sup>

Another transporter molecule that plays a significant role in glioma biology is sodium-dependent excitatory amino acid transporter (EAAT), which is a principal glutamate transporter for maintaining glutamate balance. There are several isoforms of this transporter system that distinguishes its function with respect to tissue distribution. EAAT1 and EAAT2 are primarily astrocytic transporters, while EAAT2 is mostly expressed in axon terminals of glutaminergic neurons.<sup>27</sup> EAAT3 and EAAT4 are neuronal glutamate transporters, while a predominant expression of EAAT4 has been observed in cerebellar Purkinje cells, even though small amounts of its expression was found in a subpopulation of neurons in the forebrain.<sup>27</sup> Glutamate transporters maintain the balance of normal excitatory signaling in the brain. It has been observed that glioma and normal brain cells exhibit differential expression of glutamate transporters. A study by Robert and Sontheimer reported that under normal brain cells utilize EAAT2 for the uptake of glutamate, as in contrast to glioma cells, which alter the glutamate homeostasis, mediated by lack of expression of EAAT2. It has been hypothesized that a lack of expression of EAAT and the presence of SXC in glioma induces higher amounts of GSH activity.<sup>7,27</sup> This accounts for the cytoprotection of glioma cells and the induction of tumor growth and proliferation. This triggers the expression of multidrug resistance protein (MRPs), to remove the chemotherapeutic drug, and hence tolerance to chemotherapeutic toxicity is achieved.<sup>27</sup>

## OXIDATIVE STRESS LEADING TO INFLAMMATION IN GLIOBLASTOMA MULTIFORME

The degree of oxidative stress in a cell reflects a balance between the rate of ROS production and its activity. Increased basal oxidative stress in transformed cells makes them highly dependent on their antioxidant systems to counteract the damaging effect of ROS and this makes them susceptible to further oxidative insults.<sup>28</sup> In this concert, Nrf2 acts as one of the key players for the maintenance of oxidative stress at cellular level.<sup>5</sup> When cells are exposed to increased oxidative stress, electrophiles, or cytotoxic agents, Nrf2 (a transcription factor) becomes unleashed from the Keap1 binding and translocate to the nucleus.<sup>29</sup> There, Nrf2 transcripts antioxidant responsive element (ARE)-dependent genes to balance oxidative mediators and maintain cellular redox homeostasis.<sup>30</sup> In contrast, Keap1 operates as a molecular switch for activation of Nrf2 since Keap1 can sense and transmit oxidative challenges. Thereby, Keap1 can turn the Nrf2-mediated response on- and off-dependent on the intracellular redox status.<sup>25</sup>

Nuclear factor (erythroid-derived)-like 2 has many target genes, such as, intracellular redox-balancing proteins like glutamate-cysteine ligase, heme oxygenase-1 (HEM-1) and glutathione peroxidases (GPX), phase II detoxifying enzymes like glutathione-S-transferase (GST), NAD(P)H quinone oxidoreductase-1 (NQO1), superoxide dismutase (SOD), and multidrug resistance-associated proteins.<sup>31</sup> These antioxidant enzymatic molecules have a critical role in cellular defense mechanisms. Over the past few years, the bi-faceted role of Nrf-2 has perceived widespread interest in the context of cancer onset and progression.<sup>32</sup> There is a strong notion that increased nuclear accumulation of Nrf2 in cancer cells mediates meticulous antioxidant defense response, which further

inhibits chemotherapeutic agents and radiation, thus creating an advantageous environment for cell growth.<sup>33</sup>

It has been observed that an overexpression of nuclear factor (erythroid-derived 2)-like 2 in glioblastoma and the transcriptional influence of Nrf-2 leads to elevated expression of genes in 13.7 and 32.7% of anaplastic gliomas and glioblastoma, respectively.<sup>34</sup> There is a strong perception that ROS (and other radicals) and the epigenetic mechanisms regulate gene expression.<sup>34</sup> Nrf-2 plays an essential role to balance the intracellular level of antioxidants and free radicals. Interestingly, it was found that the majority of the epigenetic divergence of glioblastoma takes place from its precursor cells. Thereby, Nrf-2 has to befall as a potent therapeutic target for the treatment of GBM.<sup>35</sup>

### **NRF-2-MEDIATED REGULATION OF MAMMALIAN TARGET OF RAPAMYCIN (mTOR) AND SIGNAL TRANSDUCER ACTIVATING TRANSCRIPTION FACTOR 3 (STAT3)**

Mammalian target of rapamycin, a key mediator of PI3K signaling, has emerged as an influential molecular target in glioblastoma patients, although clinical efforts to target mTOR have not been successful.<sup>36</sup> Mammalian target of rapamycin, which is a serine–threonine kinase, can form two distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTOR complex 1 is involved in the regulation of translation, autophagy, growth, lipid biosynthesis, mitochondria, and ribosome biogenesis, whereas mTORC2 is known to control cell survival and proliferation.<sup>37</sup> A report by Bendavid et al. has observed an increase in Nrf-2 levels leads to an increase in mTOR. The transcriptional activity of NRF2 can be regulated by mTOR inhibitors.<sup>38</sup> Temsirolimus suppressed NRF2 translocation into the nucleus in RCC4 cells, a human renal cell carcinoma (RCC) cell line.<sup>38</sup> KEAP1 is important for the transcriptional regulation of NRF2.<sup>39</sup> Structural alteration of KEAP1 and intracellular ROS promote Nrf-2 activity. Furthermore, mTORC1 can also contribute to the dissociation of KEAP1 from NRF2.<sup>40</sup> mTOR complex 1 phosphorylates serine 351 in the Keap1-interacting region (KIR) of sequestosome 1 (SQSTM1/p62).<sup>41</sup> It is not necessary for degradation of KEAP1 to occur by autophagy activation in an mTOR-dependent manner.<sup>42</sup> Conversely, NRF2 expression could take place via mTORC1 signaling activation.<sup>37</sup> Above all, earlier studies suggest that the antioxidant mechanism could be mediated by NRF2 and its expression and activation could be dependent on mTOR signaling.<sup>43</sup>

Even though there is an increased ROS level in tumor cells, mechanistic control is well-cooperated through the KEAP1–NRF2 pathway. Tumor cells are exposed to growth factors like fibroblast growth factors (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF), while normoxic conditions stimulate the activation of mTOR signaling.<sup>44</sup> Under normoxic conditions, inhibition of the mTOR signaling pathway induces radiation-sensitivity, mediated by attenuation of Nrf-2 activity via ROS.<sup>39</sup> Unlike normal oxygen conditions, hypoxia can be attributed to the formation and relocalization of new blood vessels. Mammalian target of rapamycin is a key mediator of PI3K signaling and an integrator of signal transduction and cellular metabolism has gained widespread interest in the development of targeted therapeutics in GBM. Previous preclinical and clinical studies conducted in GBM and other tumor types have illustrated

the role of inhibitors targeting the PI3K/mTOR pathway, which showed improved median survival, reduced local and metastatic growth, and tumor growth inhibition.<sup>10,43,45</sup>

### **JAK–STAT3 SIGNALING IN GLIOBLASTOMA MULTIFORME**

JAK/STAT3 signaling is closely involved in gliomagenesis. The pathway consists of four JAKs (JAKs1–3 and TYK2) and seven STATs (STATs1–4, 5a, 5b, and 6).<sup>43</sup> Of all the STATs, STAT3 is certainly the most eminent among cancers. It can be activated by various stimuli, including cytokines, growth factors, and interferons. Once an external factor has bound its receptor, JAKs are recruited to the cytoplasmic receptor tail and phosphorylate both themselves, and STAT3 is then recruited to the tail, where it is phosphorylated on tyrosine 705 (and thus activated) by JAKs. The STATs will subsequently form homo- or heterodimers and localize to the nucleus, where they modulate gene expression.<sup>43,44</sup>

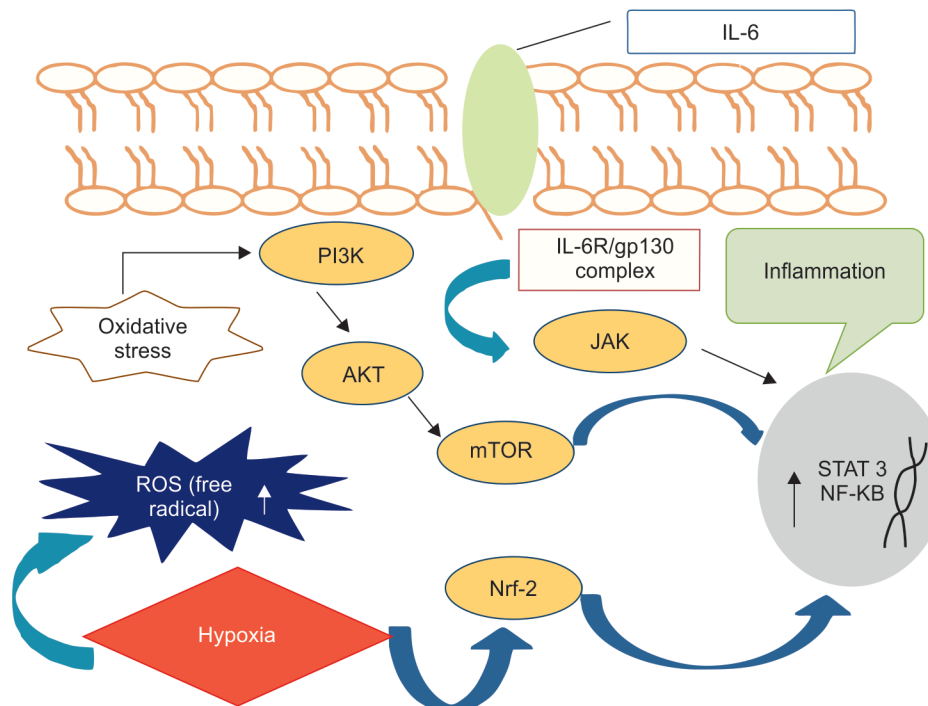
Signal transducer activating transcription factor 3 signaling is commonly activated by interleukin (IL)-6 family cytokines, including IL-6, oncostatin M (OSM), and leukemia inhibitory factor (LIF). Transcriptional activity of a set of genes associated with aspects of tumor cell survival and growth is commonly driven by STAT3.<sup>43</sup> Gray et al. reported that gene expression of STAT3 showed a preferential interesting role in non-cycling cells as well, rather from being a general driver for growth. Generally, STAT3 plays a salient role to promote tumor survival and invasion with antitumor immune suppression. Upregulated expression and nuclear accumulation of STAT3 is one of the distinguishing features of GBM, and this abrupt activation of STAT3 is correlated with poor prognosis.<sup>46</sup>

Acute inflammation in GBM is initiated by resident macrophages/mast cells of tissues to upregulate the expression of proinflammatory cytokines, chemokines, and ILs.<sup>47</sup> Tumor formation leads to the replacement of anti-inflammatory molecules by proinflammatory molecules. Furthermore, the pathogenesis of GBM initiates with chronic inflammation with the aid of these proinflammatory signaling cascades.<sup>47</sup>

Chronic inflammation in GBM is associated with the infiltration of microglia, which induces expression of proinflammatory cytokines—IL-6 and IL-8 specifically, stimulated by CD4+ helper T cells to activate CD8+ cytotoxic cells, as feedback loop.<sup>48,49</sup> Interleukin binds to specific IL-R, recruiting PI3K/AKT/mTOR to JAK–STAT3 which is a major contributor in inflammation, adding to pathogenesis in GBM (shown in Figure 1). It has been reported that constitutive activation of STAT3 is influenced by different signaling molecules like EGFR, heregulin-2/neuregulin receptor (Her2/Neu), platelet-PDGFR, IL-6R/gp130, c-Met, Abelson leukemia protein (ABL), and Src tyrosine kinases.<sup>50</sup> In a nutshell, STAT3 can promote tumor development and progression via action in multiple compartments of GBM tissue, thus prominently displaying STAT3's clinical promise for this disease. Inhibition of JAK/STAT3 signaling has been of considerable interest in clinical and preclinical studies.<sup>51</sup> The most common type of specific JAK/STAT inhibitors to date has been small-molecule JAK inhibitors, and many of these have had positive results in studies of GBM *in vitro* and *in vivo*. Thus, STAT3 inhibition may prove to be one of the effective strategies for the therapeutic effect of GBM.<sup>52</sup>

### **THERAPEUTIC TARGETS IN GBM**

The influence of the PI3K/AKT/mTOR pathway in cell survival of GBM suggests that its inhibition may lead to an increase in apoptosis.<sup>53</sup>



**Fig. 1:** Diagrammatic representation of mediators in oxidative stress and inflammation. IL-6 binds to IL-R/gp 130 complex which induces STAT3 expression via Janus-kinases (JAK). Concurrently, Nrf-2 plays bi-faceted role in GBM. Nrf-2 transmits either by mTOR or STAT3 to stimulate the inflammatory pathway

Thus, inhibition of this pathway could help in therapeutic value in GBM.<sup>54,55</sup> Below is the list of few drugs that inhibit this pathway in GBM.

Trimebutine, a prokinetic agent, which is widely used to treat gastrointestinal disorders, has shown to inhibit growth, proliferation, and migration of GBM cells and promotes cell apoptosis via reducing the activation of MAPK/ERK and PI3K/AKT signaling pathway *in vitro* (SHG44, U251, and U87 MG) and *in vivo*.<sup>56</sup> Similarly, a study by Liu et al. revealed that celastrol, a triterpene compound derived from the traditional Chinese medicine *Tripterygium wilfordii*, ceases the G2/M phase of the cell cycle and triggers autophagy and apoptosis by inducing JNK/ROS signaling, followed by blocking the AKT/mTOR signaling pathway in human and murine glioma cell lines, respectively.<sup>57</sup> Recently, a study by Lu et al. reported that tumor necrosis factor (TNF- $\alpha$ ) was found to elevate the apoptotic rate in glioma cells by inducing the mitochondrial fission and downregulating the MAPK-ERK-YAP signaling. This finding defines that mitochondrial fission may act as a tumor suppressor which implicates for a potential therapeutic approach in GBM.<sup>58</sup>

Raddeanin (RA), an active pharmacological component isolated from *Anemone raddeana* regel, induces apoptosis by an increase in the production of intracellular ROS and activation of Jun N-terminal kinase (JNK) in an *in vitro* study.<sup>59</sup> It has also shown that RA could induce autophagy in GBM cell lines and inhibits GBM in BALB/C nude mice.<sup>59</sup>

Yang et al. have reported a novel inhibitor, Tanshinone IIA, which is extracted from *Salvia miltiorrhiza* Bunge was found to exhibit an inhibitory effect on glioma stem cells (GSCs) by suppression of proliferation, attenuation of stemness, and induction of apoptosis via downregulating the IL6/STAT3 signaling pathway.<sup>60</sup>

Chinese traditional medicines are also found to play a key role in inhibiting the growth of GBM cells. Brevilin A, a sesquiterpene

lactone component of *Centipeda minima*, was found to induce mitochondrial-mediated apoptosis associated with the induction of oxidative stress in glioma cells.<sup>61</sup> Another interesting compound, Shikonin, a naphthoquinone with antitumor properties has proven to be a powerful new tool for GBM treatment by reducing therapy resistance and tumor recurrence.<sup>62</sup>

Many plant components and products are rich in phytochemicals, such as, flavonoids and alkaloids, which are found to possess anticancer activities.<sup>63</sup> Baicalein (BA), a flavonoid compound, derived from the roots of *Scutellaria baicalensis* has shown to induce apoptosis via inhibiting the activity of NF $\kappa$ B-p65, suggesting that it could be used as a potential therapeutic agent against GBM.<sup>64</sup> Another alkaloid, which is derived from cortex lycii radices, Kukoamine A (KuA), has been reported to possess antioxidant and anti-inflammatory activity. The study showed that KuA significantly decreased proliferation, migration, and invasion colony formation of GBM cells.<sup>65</sup> Recently, a small molecule termed as RIPGBM that acted as a molecular switch was found to modulate receptor-interacting protein kinase 2 (RIPK2), resulting in caspase-1-mediated apoptosis in GBM CSCs and reduces the tumor growth in an intracranial xenograft model.<sup>66</sup> Similarly, various extract of natural products or product analogs that can modulate the blood-brain barrier permeability and induce cell death GBM have been widely reported.<sup>67</sup> Furthermore, several drugs in combination with other therapies aimed at molecular targets have been in different phases of clinical trials. Clinical outcomes targeting molecular markers in GBM have been described (Table 1).

Therefore, it is not surprising that the reuse of old drugs or already existing drugs are gaining importance from the point of molecular pharmacology. Drug repurposing or cancer-related drugs have shown valuable experimental evidence as antineoplastic agents.<sup>75</sup> A few of them have been explained to exemplify the concept of drug repurposing in cancer therapy.

**Table 1:** Molecular markers targeted in glioblastoma multiforme and clinical outcomes

Markers	Genetic/epigenetic alteration	Pathway affected	Prognosis
MGMT	Promoter methylation	DNA mismatch repair	Better <sup>68</sup>
EGFR	Gene mutation/partial deletion (EGFRΔIII)	PI3K/AKT/MAPK	Poor <sup>13</sup>
IDH1	Point mutation (R132H)	G-CIMP and metabolic alteration	Better <sup>14</sup>
G-CIMP	Hypermethylation	Global epigenetic alteration	Better <sup>69</sup>
ATRX	Gene mutation	Alternative telomere lengthening	Poor <sup>18</sup>
TP53	Gene mutation	p53	Unknown <sup>70</sup>
PTEN	Gene mutation	PI3K/AKT/MAPK	Poor <sup>71</sup>
1p19q deletion	CIC and FUBP mutation	Not clearly known	Better <sup>72</sup>
SRC	Phosphorylation	Integrin signaling	Better <sup>73</sup>
RPS6	Phosphorylation	mTOR	Poor <sup>74</sup>

### Disulfiram

Disulfiram is an aldehyde-dehydrogenase 1 (ALDH1) inhibitor, which catalyzes the conversion of acetic acid from ethanol. Disulfiram is involved in resistance toward TMZ in GBM. Acetic acid is an essential metabolite in Krebs's cycle and plays a key role in the upsurge of brain metastasis.<sup>76,77</sup> In recent years, disulfiram has been involved in clinical trials in combination with other drugs in GBM.<sup>78</sup>

### Rapamycin

Rapamycin, a prominent and widely known antifungal drug that has shown comprehensive pharmacological activity, especially in the inhibition of mTOR complex 1.<sup>79</sup> Abbruzzese et al. reported that rapamycin and its derivatives are gaining extensive interests, as they are already in the clinical trials. Cancer cells display a complicated interplay of signaling molecules. In the field of anticancer therapeutics, drugs targeted at metabolic pathways have been a center of attention.<sup>80</sup> A wide known antidiabetic drug, metformin operates through AMP kinase/mTORC1. Metformin has now been used as an adjuvant in cancer therapy and is presently in clinical trials in association with other drugs for GBM.<sup>81,82</sup>

Not only antidiabetic and cardiovascular drugs, but antipsychotic agents are also used to treat GBM in combination with standard care of drugs.<sup>83</sup> One such drug is, chlorpromazine (CPZ), which acts as a potent and specific inhibitor of mitotic kinesin KSP/Eg5, thereby inhibiting AKT/mTOR, eliciting autophagic cell death in human glioma cells.<sup>78</sup> In this notion, antipsychotic agents can be considered for anti-GBM therapeutics to prove the efficacy of these intelligent drugs.

Likewise, an antifibrinolytic drug has also proven to be effective as antitumor agents. Upamostat, a small molecule urokinase-type plasminogen activators (uPA)-targeted inhibitor, approved by

FDA has been used against the treatment for pancreatic cancer.<sup>84</sup> Since there has been a cross-talk of fibrinolysis and inflammation, existing non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to act as potential antiglioma agents, since inflammation is a mandatory and convoluted mechanism for GBM.<sup>85</sup>

### CONCLUSION

Glioblastoma multiforme is one of the dreadful and aggressive forms of brain tumors. Etiology and treatment for GBM is a complicated task from the context of histological grades of this tumor. Glioblastoma multiforme exhibits several cellular and molecular processes, such as, augmented proliferation, imbalanced redox environment, immune evasion, immunosuppression, and inflammation. Oxidative stress-mediated by PI3K/AKT/mTOR can be modulated by mTOR and Nrf-2, which in turn stimulates STAT3. Thereby, activation of STAT3 can be regulated by targeting mTOR or JAK. Activation of JAK/STAT3 is also facilitated by proinflammatory molecules like ILs, chemokines, and even growth factors. These signaling molecules induce the upregulation of genes involved in proliferation, invasion, differentiation, and inflammation. As of now, each of these molecules has served as an important therapeutic drug target. Deregulation of the immune system in CNS and the development of inflammation associated with the malignant stage of glioma remains to be answered. Of late, there is a need to improve treatment strategy with a focus on several molecular targets, with a concern for a better prognosis for cancer patients.

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