



Review

SUMOylation in Glioblastoma: A Novel Therapeutic Target

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Abstract: Protein SUMOylation is a dynamic post-translational modification which is involved in a diverse set of physiologic processes throughout the cell. Of note, SUMOylation also plays a role in the pathobiology of a myriad of cancers, one of which is glioblastoma (GBM). Accordingly, herein, we review core aspects of SUMOylation as it relates to GBM and in so doing highlight putative methods/modalities capable of therapeutically engaging the pathway for treatment of this deadly neoplasm.

Keywords: glioblastoma (GBM); SUMOylation; SUMO1-3; post-translational modifications (PTMs)

1. Introduction

Glioblastoma (GBM), a WHO grade IV glioma, represents the most common primary brain tumor in the adult population. The current standard of care for newly diagnosed GBM includes maximal safe surgical resection with concomitant radiation followed by adjuvant chemotherapy with the alkylating drug temozolomide, which may now be combined with intermediate-frequency alternating electrical fields [1]. Unfortunately, these tumors have a dismal prognosis with a median overall survival of only 10–20 months, and individual survival rarely exceeds two years [2]. GBM is an extremely invasive and malignant tumor with a litany of characteristics that impede effective clinical treatment (e.g., GBMs are highly vascular, rapidly dividing tumors that commonly recur despite aggressive multimodal treatment regimens) [2,3]. Accordingly, new approaches to treatment are vital in an attempt to improve outcomes. An improved understanding of molecular pathways within these highly heterogeneous tumors may ultimately provide detailed insight into the driving forces behind GBM's unusually

aggressive and treatment-resistant nature. In line with such thinking, herein, we examine protein post-translational modification (PTM) with small ubiquitin-like modifier (SUMO) in the setting of GBM and discuss the therapeutic potential of targeting this pathway as a novel treatment paradigm for this devastating tumor of the central nervous system (CNS).

2. SUMOylation

The regulation of cellular physiology is coordinated in part by control of protein activity, abundance, localization, and/or interactions via a variety of reversible PTMs (e.g., SUMO, phosphorylation, and ubiquitin). SUMO is a protein with ~18% homology to ubiquitin. The conjugation of SUMO has been termed SUMOylation. It is an essential PTM that is highly conserved among eukaryotic organisms [4,5]. SUMOylation occurs at a similar frequency to other major PTMs, with greater than 3600 SUMOylated human proteins identified to date [6]. Specifically, many proteins related to both the cell cycle and DNA repair pathways are known SUMOylation targets, and accordingly, this PTM plays a key role in the maintenance of genomic stability, leading to considerable interest in understanding the SUMO pathway in cancer [7–9]. The SUMO proteins are ~100 amino acids in length and have considerable structural overlap with ubiquitin, despite limited sequence homology [10]. In mammals, there are four known SUMO isoforms: SUMOs 1–4 [4,11–17]. SUMO-2 and SUMO-3 share ~95% homology and display a great deal of functional overlap [18]. However, SUMO-2 expression is considerably higher than SUMO-3, and SUMO-2 knockout mice are embryonically lethal while SUMO-3 knockout mice are phenotypically normal [19]. SUMO-1 has ~50% homology with SUMO-2/3 and is also expressed at markedly lower levels than SUMO-2 [18,19]. SUMO-1 knockout mice are viable, yet there is an adult phenotype suggesting that SUMO-2/3 can compensate for the loss of SUMO-1 in development but not in all physiological functions [20–23]. While SUMO-1 and SUMO-2/3 have both distinct as well as shared protein substrates and their conjugation dynamics vary through the cell cycle and in response to stressors [24]. SUMO-4, the least studied SUMO isoform, displays ~86% homology with SUMO-2 and likely does not mature or undergo conjugation under normal conditions [25]. Despite this, several studies have suggested that SUMO-4 is in fact conjugated under select conditions of biological stress [26,27].

As ubiquitin-like proteins, the enzymatic cascade responsible for SUMO processing and conjugation are similar to those of ubiquitination. SUMO proteins are translated in an inactive form that undergoes maturation via endopeptidase cleavage by SUMO-specific proteases, also known as sentrin-specific proteases (SENPs) prior to entering the conjugation cascade [28,29]. The proteins that participate in SUMO conjugation are classified as E1 activating enzymes, an E2 conjugation protein, and E3 target protein ligases. Conjugation begins with activation of mature SUMO by the E1 complex, a heterodimer of SUMO-activating enzyme 1 and 2 (SAE1, SAE2) [24,30]. Activation proceeds via a two-step ATP-dependent reaction that concludes with a high-energy thioester bond between the C-terminus of SUMO and the E1 complex [31]. Following activation, the SUMO-specific conjugating enzyme Ubc9, the sole E2, binds to E1-SUMO intermediate via an interaction with SAE2 [32,33]. Next, SUMO is transferred from the E1 complex to the cysteine residue of the Ubc9 active site, and subsequently, Ubc9 catalyzes the formation of an isopeptide bond with a lysine residue of the substrate protein, thus completing conjugation [34–36]. Notably, Ubc9 facilitates substrate targeting through recognition of a consensus motif that includes the target lysine [37,38]. In a substrate-specific manner, the final step of conjugation may also require the assistance of an E3 protein ligase to facilitate interaction of Ubc9 with substrate. Human SUMO E3 ligases include the protein inhibitor of activated STAT (PIAS) family and RanBP3, both of which function with a wide variety of substrates, as well as a variety of other E3 ligases that function with a narrower collection of substrate proteins [39–42]. The final component of the SUMOylation pathway is deconjugation or deSUMOylation. Like maturation, deconjugation is catalyzed by SENPs, albeit via isopeptidase activity instead of endopeptidase activity [28,29]. Importantly, the balance between SUMO conjugation and deconjugation determines protein SUMOylation status, and this process is in part controlled by

the regulation of the activity and localization of SENPs [43]. In humans, there are six SENPs, SENP1-3 and SENP5-7 [44,45]. Additionally, two other SUMO-specific proteases, USPL1 and DeSI1, have been identified, though the scale of their role in broader de-SUMOylation appears to be limited [46,47]. Individual SENPs exhibit unique SUMO protein specificity, localization, and affinity for endopeptidase versus isopeptidase activity.

3. SUMOylation and Cancer

In cancer, dysregulation of PTMs plays an important role in the pathologic cellular processes that underlie malignant transformation and progression. SUMOylation was first associated with cancer not long after its discovery, with the identification of promyelocytic leukemia protein (PML) as one of the first known SUMOylation substrates [48]. In acute promyelocytic leukemia (APL), a chromosomal translocation involving chromosomes 15 and 17 leads to the creation of the PML-retinoic acid receptor- α (PML-RAR α) fusion oncoprotein [49,50]. Pathologic APL blasts are deficient in structures known as PML nuclear bodies, which require SUMOylation of PML in order to form [51]. Curative treatment of APL is accomplished with arsenic compounds that cause poly-SUMOylation of PML-RAR α , which facilitates degradation of the oncoprotein and restoration of PML bodies [52–54]. These discoveries in APL provided an important proof-of-concept for the role of SUMOylation in cancer and opened the door for a broad investigation into the PTM's role in many other cancers.

Genomic stability is maintained through the coordinated action of both the DNA damage response (DDR) and cell cycle regulation. These vital cellular processes prevent the accumulation and passage of somatic mutations and safeguard against malignant transformation. DNA replication and repair proteins are critical functional components of the DDR, and many of these proteins are known to be SUMOylation substrates [55]. Additionally, the SUMOylation of DDR proteins increases in response to DNA damage, and further, functionally necessary SUMOylation events have been identified in the setting of DNA repair [56–60]. Normal cell cycle regulation also requires the SUMOylation pathway, with many cyclins and cyclin-dependent kinases (CDKs) having been identified as SUMOylation substrates [61–63]. In the setting of cancer, dysregulated SUMOylation of CDKs prevents normal ubiquitin-mediated degradation, thus allowing CDK persistence and pathological cell cycle progression [64]. Finally, many oncoproteins and tumor suppressors promote carcinogenesis through the enhancement, absence, or dysfunction of their actions in the cell cycle or the DDR, and SUMOylation has been implicated in the function of a number of these cancer-associated proteins including p53, RB, BRCA1, MYC, MDM2, and cyclin D1 [59,65–69]. Taken together, prior studies have established a critical role of the SUMOylation pathway in the maintenance of genomic stability and have highlighted that dysregulated SUMOylation places genomic integrity at risk.

A growing body of evidence supports the concept that SUMOylation is broadly enhanced in many types of cancer. Upregulation of SUMO proteins, SUMOylation machinery (e.g., Ubc9), and SUMO ligases have been identified in a variety of malignancies including brain, lung, GI, liver, pancreas, breast, prostate and skin as well as lymphoma and multiple myeloma [64,70–79]. While upregulation of the SUMOylation pathway appears the predominant perturbation in the setting of cancer, it is prudent to note that downregulation has been reported [76]. Further, upregulation of SUMO-specific proteases in various malignancies suggests that dysregulation of de-SUMOylation is also present in numerous cancers [7,80]. Considering the robust alteration in the SUMOylation pathway across diverse cancers, it is perhaps not surprising that many of the defining characteristics of malignancy have been linked to SUMOylation, including apoptotic resistance, replicative immortality, angiogenesis, invasion, and metastasis [69,81–84]. Considering these multi-level biological connections between SUMOylation and cancer that extend across diverse malignancies, it is plausible that dysregulated SUMOylation is fundamental in malignancy, and it has been proposed that SUMOylation-mediated stress resistance may thus represent a unifying characteristic [80,85].

4. SUMOylation in Glioblastoma

As noted above, GBM continues to portend a dismal prognosis despite an improved understanding of the underlying biology of GBM at the molecular level (e.g., IDH1 mutational status and *MGMT* methylation status). Research advances in GBM have revealed that a multitude of cellular signaling pathways are dramatically altered by the disease, and due to this complexity, targeting cellular signaling pathways with wide-ranging biological actions, such as PTMs, may be necessary to achieve more robust treatment responses [86]. As SUMOylation targets thousands of proteins and participates in many critical cellular processes, especially in conditions of stress, this PTM may represent such a target.

Astrocytic malignancies, including GBM, were one of the first cancers in which global upregulation of SUMOylation was identified [70]. Yang et al. demonstrated a nearly 30-fold increase in the level of SUMO-1 and SUMO-2/3 conjugated proteins in patient-derived GBM samples. SUMOylation was also significantly upregulated in grade II and III astrocytomas but was highest in GBM [70]. Importantly, upregulation of SUMOylation in GBM has since been replicated in both patient samples and multiple human GBM cell lines [64,87]. Components of the SUMOylation pathway are also upregulated in both GBM samples and cell lines, including E1 (SAE1), E2 (Ubc9), and E3 (PIAS1 and 3) components as well as a SUMO-specific protease (SEN1) (Figure 1) [64,70,88–90]. Taken together, these studies provide strong evidence that SUMOylation is enhanced/aberrant in GBM.

To initially characterize the role of upregulated SUMOylation in GBM, Yang et al. utilized gene silencing of SUMO-1-3 and demonstrated disruption of DNA synthesis and cell growth as well as decreased clonogenic survival [70]. This study additionally found that silencing SUMO-1-3 in GBM interfered with the DDR, specifically double-strand break repair, which is consistent with prior studies of SUMOylation in DNA repair mechanisms [70]. This deficiency suggests that enhancement of SUMOylation acts to protect GBM cells from DNA damage, thus promoting survival and potentially contributing to radiation resistance. To this effect, Soars et al. examined the impact of the SUMOylation pathway on GBM sensitivity to radiation. They demonstrated upregulation of the SUMO-specific E3 ligase PIAS1 in a human GBM cell line and showed that radiation causes PIAS1 to interact with stress-inducible phosphoprotein 1 (STI1) leading to the protein's nuclear accumulation and ultimately resistance to radiation-induced cell death [88]. Together these studies implicate upregulation of the SUMOylation pathway in pro-survival processes and suggest that the pathway may contribute to radioresistance in GBM.

The SUMOylation pathway is known to contribute to cell cycle regulation via the SUMOylation of cyclins and CDKs [61–63]. Bellail et al. demonstrated that activation SUMOylation in GBM leads to SUMO-1 adduction to CDK6 [64]. Under normal conditions, CDK6 ubiquitination and proteasomal degradation lead to controlled cell cycle arrest at the G1 checkpoint [91]. In GBM, SUMO-1 modified CDK6 does not undergo ubiquitination, and as a result, the protein is stabilized and drives the cell cycle through the G1-S transition. This process releases the brake on the cell cycle in GBM, as knockdown of either SUMO-1 or CDK6 in GBM cells or xenografts leads to growth inhibition. Further, patient samples were found to have elevations in both SUMO-1 and CDK6 [64]. In support of these findings, we confirmed the SUMO-1-CDK6 interaction in GBM cells and demonstrated that small molecule-mediated inhibition of SUMOylation can decrease in CDK6 levels in multiple human GBM cell lines [87]. Of note, the decrease in CDK6 in response to inhibition of SUMOylation was mediated by proteasomal degradation, consistent with the mechanism that SUMO-1 conjugation to CDK6 prevents its ubiquitin-mediated degradation [87]. Together these studies demonstrate that enhanced SUMOylation in GBM acts directly on the cell cycle, ultimately leading to uncontrolled tumor growth.

Glioblastoma

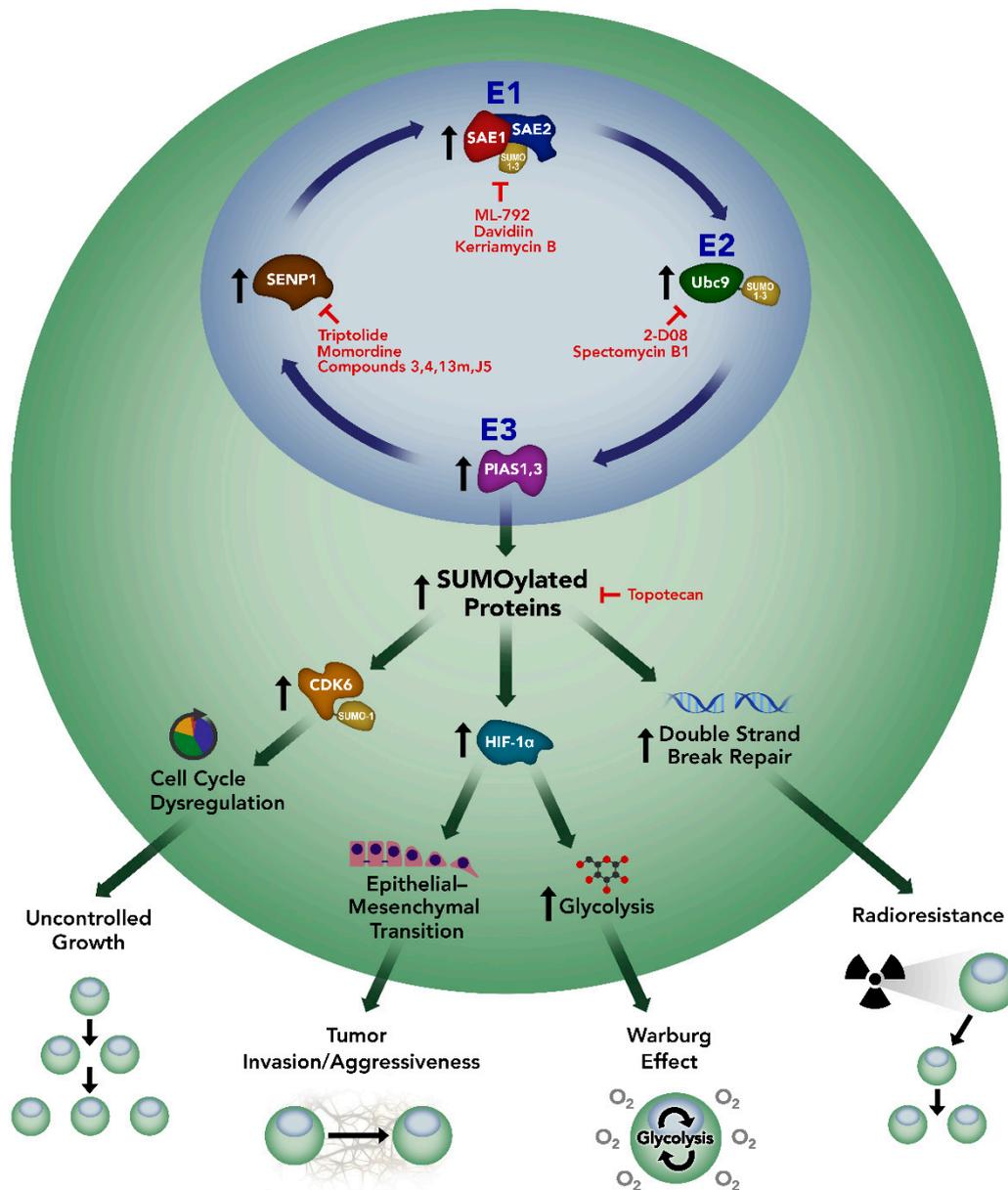


Figure 1. Enhancement of SUMOylation in glioblastoma contributes to alterations in multiple cellular processes leading to an increased malignant phenotype. Glioblastoma displays an increase in E1 (SAE1), E2 (Ubc9), and E3 (PIAS1 and PIAS3) enzymes leading to global enhancement of SUMOylation and a resultant increase in the SUMOylation level of target proteins. Further, increased expression of SUMO-specific protease (SENP1) has been reported in glioblastoma. Presently, studies have implicated CDK6 and HIF-1 α as important loci downstream of these effects that together contribute to cell cycle dysregulation, epithelial-mesenchymal transition, and heightened glycolytic metabolism. DNA double-strand break repair has additionally been associated with perturbations in SUMOylation. Together, these altered cellular processes give rise to an enhanced malignant phenotype in glioblastoma including uncontrolled growth, increased invasion and aggressiveness, a malignant bioenergetics profile with Warburg effect, and resistance to ionizing radiation. Targeting SUMOylation may represent a therapeutic approach to reverse the pathologic consequences of enhanced SUMOylation in glioblastoma. Available therapeutic agents known to inhibit SUMOylation are identified along with their targets in the SUMOylation pathway.

As a PTM with thousands of substrates, SUMOylation is known to affect a multitude of cellular processes. In an effort to examine how SUMOylation modifies the functional landscape of GBM we recently utilized liquid chromatography (LC)/mass spectrometry (MS)/MS analysis to examine changes in SUMO-1 conjugated proteins in response to inhibition of SUMOylation [87]. This analysis revealed multiple pathways that are affected by SUMOylation in GBM including DNA double-strand break repair and apoptosis signaling, consistent with prior studies [70,87,88]. However, the analysis also revealed that in GBM SUMOylation alters cellular metabolism through enhancement of glycolysis and the pentose-phosphate pathway, consistent with prior studies of SUMOylation-mediated effects on metabolism as well as the bioenergetics phenotype of GBM [92–94]. These alterations were likely related to the effect of SUMOylation on hypoxia-inducible factor-1 (HIF-1 α) that was demonstrated in the study. Of note, the SUMOylation-mediated stabilization of HIF-1 α identified in the study may also have implications for GBM progression via its effect on epithelial-mesenchymal transitions (EMT). HIF-1 α promotes EMT-associated protein expression, and in GBM, EMT is associated with progression and acquisition of a highly invasive phenotype [95–97]. Finally, we also demonstrated that in human GBM tissue samples there is wide variation in global SUMOylation levels [87]. Differences in SUMOylation and resultant downstream effects, as discussed above, may in part explain phenotypic differences between patients, such as the presence of an aggressive mesenchyme phenotype. Thus, assessment of SUMOylation status may ultimately aid in prognostication and/or in future personalized GBM therapies.

5. Targeting SUMOylation in Glioblastoma

Because of the important role SUMOylation plays in GBM, the pathway has significant potential as a novel therapeutic target to treat this intractable malignant neoplasm. Critically, several new natural and synthetic small molecule inhibitors of SENPs, SAE1, and Ubc9 have been described in the literature [29,98–102]. Although many are new and/or still in early experimental phases, they have significant potential, and several studies have explored the effect of targeting key proteins in SUMOylation in astrocytoma and GBM.

Several Food and Drug Administration (FDA) approved drugs have been assessed as SUMOylation pathway targets. Topotecan is a semisynthetic water-soluble drug from the camptothecin family with current approval for the treatment of several cancers (e.g., small cell lung cancer, cervical, ovarian) [103,104]; it is primarily a DNA topoisomerase I inhibitor. However, it also modulates the SUMOylation status of its primary target and has been shown to inhibit HIF-1 α [105–107]. In GBM, topotecan was recently found to inhibit global SUMOylation and as a result, reduce both levels of CDK6 and HIF-1 α thereby inducing pronounced changes in cell cycle progression and cellular metabolism [87].

Several other drugs have also been identified that interact with the SUMOylation pathway [29,85,98,108–110]. Although many of these have no data in GBM models as of yet, they all harbor potential as therapeutic targets in GBM. Spectomycin B1 has also been identified as a SUMOylation inhibitor by directly binding Ubc9 [108]. SAE1/2 inhibitors, such as ML-792 have been shown to potently inhibit SUMOylation with a promising application in treating MYC-amplified malignancies [111,112]. Other SAE1 targets that result in SUMOylation inhibition include ginkgolic acid [113], kerramycin B [114], davidiin [115], and tannic acid [116].

Of note, the rational design of SENP inhibitors is also technically possible [29]. Xia et al. showed that downregulation of SENP1 in astrocytoma and GBM led to inhibition of the phosphorylation of I κ B α and Akt, and also the expression of its downstream regulation factors Bcl-xL and cyclinD1 [90]. Drugs or biologic agents designed to target inhibition of SENP1 could thus promote and induce apoptosis in GBM by regulating NF- κ B/Akt pathways. Other SENP1 inhibitors that have been identified, albeit without data in GBM, include triptolide [99], momordine [117], compound J5, compound 4, compound 3, and compound 13m [98].

Beyond small molecules, genetic manipulation of the pathway is also feasible. MicroRNAs (e.g., miRNA-182 and 183) have been shown to suppress the SUMOylation pathway and as such, harbor pharmaceutical potential in malignancies defined by upregulation [110]. Mechanistically, activation of SUMO requires ATP condensation of its C-terminal tail [118]. This important step is catalyzed by SAE which recognizes the C-terminus [118]. Zhao et al. described using phage display to show that a broad profile of SUMO C-terminal sequences could be activated by SAE [119]. They subsequently developed SUMO-mimicking peptides that were conjugated to SAE and Ubc9 and blocked full-length SUMO from entering the cascade [119]. Such strategies represent further examples of how SUMOylation may be targeted for therapeutic benefit in GBM.

6. Conclusions

GBM is the most common/aggressive primary CNS tumor within the adult population, and there have been limited advances to improve outcomes for this deadly malignancy [2]. Accordingly, there is a great need to develop novel therapeutic approaches to reduce overall morbidity and mortality for GBM patients. SUMOylation, which plays an important role in a myriad of normal cellular processes and is involved in maintaining cellular homeostasis, has also been shown to play a vital role in pathological processes (e.g., allowing CNS tumors to resist/withstand stressful conditions for cell survival and continued growth) [70,87]. Accordingly, inhibition of SUMOylation in GBM provides opportunities for the development of novel therapeutics and therefore warrants continued investigation.

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