Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2024, 16(2), 70-83
https://ijbc.ir

Review Article

Molecular Pathways of Gliomas Involving RNA-Binding Protein Dynamics

Saman Batool [1], Hamza Tanveer [2], Faisal Naeem Bandesha [3], Asma Sarfraz [4*]

[1] Gomal Centre of Biochemistry and Biotechnology, Gomal University, D.I.Khan, Pakistan.
[2] Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan.
[3] Department OF Forensic Medicine and Toxicology, Post Graduate Medical Institute, Lahore, Pakistan.
[4] Shifa Tameer-e-Millat University of Pharmaceutical Sciences, Islamabad, Pakistan.

Scan and read the article online

Citation Batool S, Tanveer H, Bandesha FN, Sarfraz A. Molecular pathways of gliomas involving RNA-binding protein dynamics. Iran J Blood Cancer. 2024 June 30;16(2):70-83.

doi 0

Article info:

Received: 11 Apr 2024
Accepted: 15 Jun 2024
Published: 30 Jun 2024

Keywords:

RNA-binding proteins
Gliomas
post-transcriptional regulation
Oncogenetic pathways
RBP Methylation

Abstract

Gliomas are malignant brain tumors with complicated molecular changes contributing to their aggressiveness and limited treatment choices. RNA-binding proteins are important in post-transcriptional regulation, altering gene expression and impacting glioma formation. In this review article, we will deliberate different molecular pathways of gliomas in which RNA-binding proteins are involved. Studies reveal that a few years ago, RNA-binding proteins had a causative effect on various cancer types such as leukemia, glioblastoma, intestinal, renal, etc. RNA-binding proteins have surfaced as key players in regulating post-transcriptional processes. So, we will discuss in this article Maintaining Glioma Cells Growth, RNA-binding proteins mutations, interacting with deubiquitinating enzymes, RBP Methylation Activates Oncogenic Pathways and RNA-binding proteins in glioma subtypes, highlighting their role in tumorigenesis, invasion, angiogenesis, and therapeutic resistance.

Abbreviation list: **ATP:** Adenosine triphosphate; **DNA:** Deoxyribonucleic acid; **DUB:** Deubiquitinating enzyme; **USP:** Ubiquitin-specific protease; **UPS:** Ubiquitin-proteasome system; **CFIm:** Cleavage Factor I; **CPSF:** Cleavage and polyadenylation specificity factor; **CstF:** Cleavage stimulation factor; **CFIIm:** Cleavage factor II; **EMT:** Epithelial-to-mesenchymal transition; **GBM:** Glioblastoma multiforme; **GSC:** Glioma stem cell; **MAPK:** Mitogen-activated protein kinase; **NF-kB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **NFKBIZ:** NF-kB inhibitor zeta; **ORF:** Open reading frames; **PI3K-Akt:** Phosphatidylinositol-3-kinase-protein kinase B; **RBP:** RNA-binding protein; **RG4s:** RNA G-quadruplexes; **RTK:** Receptor tyrosine kinase; **SRSF3:** Serine/arginine-rich splicing factor 3; **TGF-β:** Transforming growth factor beta; **TAK1:** TGF-β-activated kinase 1; **TMZ:** Temozolomide; **UTR:** Untranslated region; **VM:** Vascular mimicry; **APA:** Alternative polyadenylation; **RBP:** RNA-binding protein; **ORF:** Open reading frame; **RBFOX1:** RNA binding protein, Fox-1 homolog 1; **SRSF3:** Serine/arginine-rich splicing factor 3; **BUD13:** BUD13 homolog (yeast); **CDK12:** Cyclin-dependent kinase 12; **MBNL1:** Muscle blind like splicing regulator 1; **COL1A1:** Collagen type I alpha 1 chain; **COL1A2:** Collagen type I alpha 2 chain; **COL3A1:** Collagen type III alpha 1 chain; **COL4A1:** Collagen type IV alpha 1 chain; **COL4A2:** Collagen type IV alpha 2 chain; **COL5A2:** Collagen type V alpha 2 chain; **ECM:** Extracellular matrix; **EGFR:** Epidermal growth factor receptor; **circRNA:** Circular RNA; **miRNA:** MicroRNA; **circ-SHPRH:** Circular RNA-SHPRH; **circ-HIPK3:** Circular RNA-HIPK3; **IGF2BP3:** Insulin-like growth factor 2 mRNA-binding protein 3; **FZD7:** Frizzled class receptor 7; **CFIm25:** Cleavage and polyadenylation specificity factor subunit 25; **CFIm68:** Cleavage and polyadenylation specificity factor subunit 68; **hnRNP H/F:** Heterogeneous nuclear ribonucleoprotein H/F; **eIF4E:** Eukaryotic translation initiation factor 4E; **A-Raf:** v-raf murine sarcoma 3611 viral oncogene homolog A; **MEK-ERK:** Mitogen-activated protein kinase kinase-extracellular signal-regulated kinase; **RG4s:** RNA G-quadruplexes; **IRES:** Internal ribosome entry site; **FOXP1:** Forkhead box P1; **FOXP2:** Forkhead box P2; **FZD7:** Frizzled class receptor 7

* Corresponding Author:
Asma Sarfraz
Affiliation: Shifa Tameer-e-Millat University of Pharmaceutical Sciences, Islamabad, Pakistan.
E-mail: **asmasarfraz.0237.scps@gmail.com**

[DOI: 10.61186/ijbc.16.2.70]

1. INTRODUCTION

RNA-binding proteins (RBPs) are pleiotropic proteins that regulate gene expression at the post-transcriptional stage by interacting with target ribonucleic acids (RNAs) [1]. RBPs fundamentally control gene expression via post-transcriptional regulation by modulating microRNA (miRNA) processing and the alternative splicing, alternative polyadenylation, subcellular localization, stability, and translation of RNAs [2]. Gliomas are the most common and aggressive type of primary tumor, accounting for 30% of all central nervous system (CNS) tumors. RBPs are a large class of proteins interacting with transcripts in various RNA-driven processes [3]. RBPs frequently comprise structured RNA-binding domains and intrinsically disordered regions [4]. RBPs play critical roles in RNA metabolism, regulating RNA stability, alternative splicing, modification, location, and translation. RBPs are important in RNA metabolism because they regulate RNAs' stability, localization, and functional dynamics [5].

Glioma is the most prevalent primary brain tumor that is responsible for 80% of all primary malignant brain tumors and 30% of all CNS tumors. Gliomas originate from the glial cells. Glial cells are the type of cells in the brain by which neurons are surrounded. According to the World Health Organization (WHO) 2021 CNS tumors classification, gliomas are classified into adult-type diffuse gliomas, pediatric-type diffuse low-grade gliomas, pediatric-type diffuse high-grade gliomas, and circumscribed astrocytic gliomas. From 1975-2018, 62,159 patients were diagnosed with glioma. Out of the 62,159 patients, 31,922 died from 1995-2018. Despite all of the hard work and advancements in surgical procedures and radiotherapies to increase glioblastoma survival rates, the prognosis of patients with glioblastoma remains poor, with a survival rate of approximately 15 months. Despite all the hard work and advancements in surgical procedures and radiotherapies to increase glioblastoma survival rates, the prognosis of patients with glioblastoma remains poor, with a survival rate of approximately 15 months. Relapse occurs after 14 months of diagnosis of glioblastoma in almost every patient [6].

Studies in the past five years have shown that RBPs have causative roles in various types of cancers such as liver, colorectal, renal, intestinal, leukemia and others. Expression analysis shows that in 15 types of human cancers, those RBPs are dysregulated, especially downregulated, that control the post-transcriptional modifications of cancer-causing transcripts [7, 8]. Moreover, deformities in these proteins owing to genetic alterations in RBPs transcriptome fail to serve their purpose of interacting with RNAs and carrying out co- or post-transcriptional regulations [7].

Currently the research on the associations between glioblastomas or simply gliomas in concordance to RBPs is being conducted to find an ultimate major and effective therapeutic approach. Since RNAs are less complex targets than DNA in terms of disease control, thus, taking command over the factors that enhance or repress their translation into ultimate protein structures is becoming the goal of research in surge of treatment options. This can be visualized by the popularity miRNAs gained in recent years. RBPs are mostly being evaluated in terms of prognostic factors for gliomas. One study highlighted the upregulation of MOV10 RNA helicase (MOV10), circ-DICER1, Zic Family Member 4 (ZIC4), and Hsp90β in glioma cells angiogenesis. [9]. In another study to check the extent of glioma patients' survival, 8 immune associated RBPs were worked out as signature proteins. Based on these patients are prescribed with immuno or chemotherapies [10]. Regarding treatment options, 11 signature RBPs were investigated to act as prognostic factors. A prediction system of immune function was developed and the potential of these signatures as indicators of the level of drug sensitivity was analyzed [11]. Above studies show that current research in the domain of gliomas is limited mainly to the prognostic aspect. Efforts are being made to change the direction towards effective therapeutic options but that requires an extensive survey of all the molecular pathways and its details leading to gliomas. Additionally, testing each treatment option type through in-vitro and in-vivo studies is demanded. Here we present in detail each possible molecular pathway associated with gliomas' onset and progression, the most common being post-transcriptional modification defects.

2. PATHWAYS INVOLVING RBPS CAUSING GLIOMAS

2.1. Direct post-transcriptional modification of mRNAs

RBPs play a pivotal role in directly interacting with mRNAs, thereby regulating their stability, localization, and translation efficiency. Among the numerous RBPs implicated in glioma development are Human antigen R (HuR), ELAV Like RNA Binding Protein 1 (ELAVL1), members of the insulin-like growth factor 2 mRNA-binding proteins (IGF2BP) family, and Musashi proteins. For instance, HuR, an RBP, binds to AU-rich regions (AREs)

[DOI: 10.61186/ijbc.16.2.70]

within target Messenger RNAs (mRNAs), thereby stabilizing them and promoting glioma growth. An example of this is HuR's interaction with the 3' untranslated region (UTR) of Vascular endothelial growth factor (VEGF) mRNA, leading to increased stability and fostering angiogenesis in gliomas.[12]. A notable instance of this regulatory mechanism is HuR's interaction with the 3' untranslated region (UTR) of Vascular endothelial growth factor (VEGF) mRNA. By enhancing the stability of VEGF mRNA, HuR facilitates angiogenesis within gliomas, thereby contributing to their progression and aggressiveness. This multifaceted role underscores the intricate interplay between RBPs and mRNA regulation in the context of glioma pathogenesis. Similarly, HuR stabilises COX-2 mRNA, increasing COX-2 levels and glioma cell invasion and proliferation.[13]

The IGF2BP family, comprising insulin-like growth factor 2 mRNA-binding proteins 1 (IGF2BP1), insulin-like growth factor 2 mRNA-binding proteins 2 (IGF2BP2), and insulin-like growth factor 2 mRNA-binding proteins 3 (IGF2BP3), exerts its influence by interacting with and enhancing the stability of target mRNAs. Within the intricate landscape of glioma biology, IGF2BP1 emerges as a key player, demonstrating significant overexpression in glioma cells. This upregulation of IGF2BP1 levels plays a pivotal role in promoting glioma survival and invasion by stabilizing critical transcripts involved in various oncogenic signalling pathways. Through its intricate regulatory mechanisms, IGF2BP1 contributes to the dysregulated gene expression patterns characteristic of glioma progression, highlighting its potential as a therapeutic target in combating this formidable disease. [14]. IGF2BP2, through its regulatory influence on the mRNA of matrix metalloproteinase-9 (MMP-9), orchestrates a crucial aspect of glioma biology by modulating cell motility and invasion. This regulatory interaction underscores the intricate interplay between molecular mechanisms and cellular behaviour in the context of glioma progression. The stabilization of MMP-9 mRNA by IGF2BP2 highlights the multifaceted roles of RNA-binding proteins in orchestrating the complex processes underlying glioma pathogenesis. Understanding the precise mechanisms by which IGF2BP2 influences MMP-9 expression provides valuable insights into the molecular underpinnings of glioma invasiveness, offering potential avenues for therapeutic intervention aimed at mitigating tumor progression and improving patient outcomes. [15]. By stabilising cyclin D1 mRNA, IGF2BP3 enhances glioma cell proliferation and migration [16]. These findings emphasise the importance of IGF2BPs in the development and progression of gliomas.

IGF2BPs, or insulin-like growth factor 2 mRNA-binding proteins, serve as pivotal regulators of mRNA processing within the cell. Operating primarily in the nucleus, IGF2BPs engage with nascent mRNAs, initiating the formation of messenger ribonucleoprotein (mRNP) complexes. Once integrated into these complexes, IGF2BPs facilitate the export of mRNPs from the nucleus to the cytoplasm, where further processing occurs. In the cytoplasm, these mRNPs, accompanied by IGF2BPs, traverse along microtubules or other cytoskeletal structures to reach their designated subcellular destinations. Throughout this journey, IGF2BPs play a crucial role in safeguarding mRNA stability and suppressing their translation until they arrive at their intended location. This intricate regulatory mechanism orchestrated by IGF2BPs underscores their significance in governing mRNA dynamics and cellular processes. **Figure 1** is the illustration which was modified and idea was obtained from a study [17].

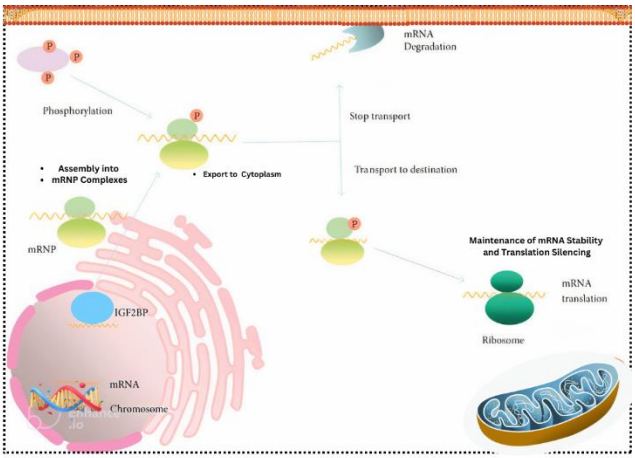

Figure 1. IGF2BPs as the Pivotal Regulators of mRNA Processing

Musashi proteins, encompassing Musashi RNA Binding Protein 1 (MSI1) and Musashi RNA Binding Protein 2 (MSI2), serve as pivotal regulators of the characteristics and self-renewal capacity of glioma stem cells. These RNA-binding proteins directly engage with target mRNAs, including Numb and cyclin-dependent kinase inhibitor 1B (CDKN1B). Specifically, MSI1 augments glioma stemness and tumorigenicity through mechanisms such as the repression of Numb mRNA translation, thereby amplifying Notch signalling and bolstering the self-renewal capabilities of glioma stem cells. This intricate regulatory network underscores the critical role of Musashi proteins in governing glioma stem cell behaviour and highlights their potential as therapeutic targets for mitigating tumor progression and enhancing treatment efficacy [18]. MSI2

[DOI: 10.61186/ijbc.16.2.70]

interacts with CDKN1B mRNA, thereby constraining its translation and fostering glioma cell proliferation [19]. Dysregulation of Musashi proteins contributes to the maintenance of glioma stem cell populations and the aggressive phenotype of gliomas.

2.2 Post-transcriptional modification of mRNAs through miRNA

RBPs play a critical role in post-transcriptional regulation through their interaction with miRNAs. MiRNAs, small non-coding RNAs, bind to target mRNAs, leading to their degradation or translational suppression. RBPs such as Argonaute RISC Catalytic Component 2 (AGO2) and Lin-28 Homolog A (LIN28A) are involved in modulating miRNA biogenesis or target recognition.

AGO2, a component of the RNA-induced silencing complex (RISC), interacts with miRNAs to facilitate their binding to target mRNAs in glioma cells. This interaction is essential for miRNA-mediated post-transcriptional regulation and can impact various aspects of glioma biology, including cell proliferation, invasion, and tumorigenesis. Acting as an effector of miRNA-mediated gene silencing, AGO2 binds to mature miRNAs, guiding them to their target mRNAs. Subsequently, this interaction leads to mRNA degradation or translational repression, thereby regulating gene expression and contributing to the development of gliomas. [14].

LIN28A, an RBP, plays a crucial role in modulating the production of let-7 miRNA. Let-7 miRNAs serve as tumor suppressors and are often downregulated in various malignancies, including gliomas. LIN28A exerts its influence by inhibiting the processing of primary let-7 miRNA transcripts, leading to reduced levels of mature let-7 miRNAs. This dysregulation creates an imbalance that promotes glioma cell proliferation, stemness, and resistance to therapy.

In gliomas, LIN28A-mediated suppression of let-7 miRNA production contributes significantly to the aggressive behaviour of tumor cells. By impeding the processing of primary let-7 miRNA transcripts, LIN28A diminishes the pool of mature let-7 miRNAs available for regulatory functions. Consequently, the decrease in let-7 miRNA levels unleashes a cascade of molecular events that fuel glioma progression. Enhanced glioma cell proliferation, augmented stemness characteristics, and heightened resistance to therapeutic interventions are among the detrimental outcomes associated with this dysregulated LIN28A-let-7 axis [20]. By inhibiting the synthesis of let-7 miRNA, LIN28A fosters the upregulation of target genes implicated in driving oncogenic pathways within gliomas. Notably, this dysregulation leads to the overexpression of key oncogenes such as Myelocytomatosis oncogene (MYC) and high mobility group A2 (HMGA2). The consequent amplification of these oncogenic signals exacerbates glioma aggressiveness, promoting cellular proliferation, invasiveness, and resistance to therapeutic interventions [21].

3. MAINTAINING GLIOMA CELL GROWTH

RBPs play a significant role in sustaining the growth of glioma cells by modulating essential signalling pathways. Numerous RBPs have been implicated in regulating the proliferation, survival, and invasion of glioma cells.

One such RBP, far upstream element-binding protein 1 (FUBP1), interacts with the MYC promoter, leading to heightened MYC expression. MYC is a renowned oncogene known for its regulatory control over fundamental cellular processes like cell development and proliferation. In the context of gliomas, the increased expression of FUBP1 exacerbates MYC overexpression, thereby fostering glioma cell proliferation and facilitating tumor progression. This interaction underscores the intricate regulatory networks orchestrated by RBPs in driving the aggressive behavior of gliomas. [22]. Additionally, FUBP1 exerts regulatory control over the expression of other genes implicated in glioma pathogenesis, including tumor protein 53 (TP53) and Cyclin D1 (CCND1). This multifaceted role highlights FUBP1's involvement in orchestrating a network of genes critical for glioma development and progression, further underscoring its significance as a potential therapeutic target in glioma treatment strategies.[23].

Cytoplasmic polyadenylation element-binding proteins (CPEBs) are RBPs that play a crucial role in regulating mRNA translation in response to various growth factors and cellular stimuli. Dysregulation of CPEBs has been associated with the initiation and progression of gliomas. One of their key functions is to modulate the length of the poly(A) tail of target mRNAs, thereby influencing translation efficiency. Specifically, cytoplasmic polyadenylation element-binding protein 1 (CPEB1) is known to exert translational control over mRNAs encoding factors essential for glioma cell proliferation, such as cyclins and cyclin-dependent kinases. This regulatory mechanism underscores the pivotal role of CPEBs in glioma pathogenesis, highlighting their potential as therapeutic targets for intervention strategies aimed at disrupting glioma cell growth and progression. [24]. CPEB1 dysfunction can result in abnormal translation regulation, contributing to the uncontrolled development of glioma cells.

[DOI: 10.61186/ijbc.16.2.70]

In the realm of glioma biology, the role of RNA modifications, particularly N6-methyladenosine (m6A) and its associated reader proteins, has emerged as a focal point of research interest in recent years. m6A stands out as the most prevalent internal mRNA modification, playing a pivotal role in the dynamic regulation of gene expression. Among the key players in this regulatory network are the YTH domain-containing proteins, namely YTHDF1 and YTHDF2, recognized as crucial readers of m6A modifications implicated in glioma progression. YTH N6-Methyladenosine RNA Binding Protein F1 (YTHDF1) functions to enhance the translation of m6A-modified mRNAs pivotal for maintaining glioma stem cell populations and promoting self-renewal capabilities. Conversely, YTH N6-Methyladenosine RNA Binding Protein F2 (YTHDF2) is involved in the degradation of m6A-modified mRNAs associated with glioma cell growth and proliferation. Dysregulation of the m6A modification and its reader proteins can disrupt the normal patterns of gene expression, thereby contributing to the initiation and advancement of gliomas. This intricate interplay between m6A modifications and their reader proteins underscores their significance in glioma pathogenesis and presents potential therapeutic targets for intervention strategies aimed at impeding glioma progression. [25].

4. RBP MUTATIONS

Mutations affecting RNA-binding proteins (RBPs) can instigate glioma development, with several RBPs displaying recurrent mutations across various glioma subtypes, including glioblastoma multiforme (GBM). These mutations often disrupt normal RNA processing mechanisms, thereby contributing to carcinogenesis. Among the frequently observed mutations in gliomas is found in the HNRNPA1 gene, encoding heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1). Mutations in HNRNPA1 have been identified in a subset of glioblastomas, leading to alterations in the RNA-binding properties of hnRNPA1. Consequently, the aberrant function of hnRNPA1 precipitates abnormal alternative splicing events, exerting a significant influence on gene expression patterns implicated in glioma growth and progression. [26]. Dysregulation of alternative splicing mechanisms can yield isoforms exhibiting oncogenic properties or lead to the loss of isoforms possessing tumor-suppressive functions, both of which play pivotal roles in glioma development.

Another RNA-binding protein (RBP) implicated in glioma-associated mutations is FUBP1 (fused in glioblastoma). Mutations in FUBP1 have been identified in gliomas, particularly in juvenile high-grade gliomas. These mutations have the potential to disrupt the normal functioning of FUBP1, affecting its RNA-binding capacity and altering gene expression profiles. FUBP1 governs the expression of MYC and other target genes crucial for glioma growth and survival. Consequently, mutations in FUBP1 can lead to dysregulated MYC expression, thereby contributing to the aggressive nature of gliomas. [27].

Gliomas have also been associated with mutations in other RNA-binding proteins (RBPs), including RNA Binding Motif Protein 10 (RBM10) and RNA Binding Motif Protein 17 (RBM17). Mutations in RBM10 have been implicated in the pathogenesis of glioblastoma and anaplastic astrocytoma. RBM10 plays a crucial role in regulating alternative splicing, and mutations in this gene can perturb the splicing patterns of genes critical for glioma development. [27] . In addition to RBM10, mutations in RNA Binding Motif Protein 17 (RBM17) have also been identified in gliomas. These mutations have been implicated in disrupting RNA processing mechanisms, which subsequently lead to changes in gene expression patterns. The aberrant gene expression profiles caused by RBM17 mutations may contribute to the development and progression of gliomas by promoting tumorigenesis. [28] .

The identification of mutations in RBPs within gliomas underscores their significance in the pathogenesis of these malignancies. These mutations can disrupt normal RNA processing mechanisms, including splicing, stability, and translation regulation, leading to the dysregulation of critical genes involved in glioma initiation and progression. Moreover, RBPs exert pivotal roles in glioma development through various mechanisms. They are involved in direct post-transcriptional mRNA modifications, orchestrate post-transcriptional mRNA modifications via miRNAs, maintain glioma cell proliferation, and contribute to the onset of gliomas through mutations. Understanding these intricate pathways provides valuable insights into the underlying molecular mechanisms driving glioma formation, offering potential targets for therapeutic intervention.

4.1. Interacting with deubiquitinating enzymes

Ubiquitination is a firmly controlled, exceedingly precise, and Adenosine triphosphate (ATP)-dependent natural procedure carried out by a multifaceted cascade of enzymes. It is a crucial trouper in protein homeostasis, allocation to quickly remove unsolicited or impaired proteins [29].

The ubiquitin-proteasome system (UPS) serves as a fundamental mechanism for maintaining protein turnover

[DOI: 10.61186/ijbc.16.2.70]

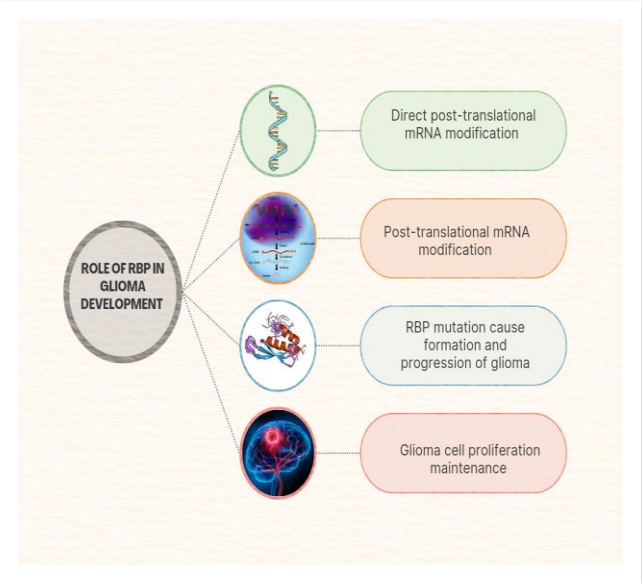

Figure 2. Role of RBPs in development of glioma.

within cells, regulating various cellular processes critical for cell function and homeostasis. Apart from its role in cell DNA repair, differentiation, and cell division, the UPS is involved in diverse biological activities such as protein quality control, signal transduction, and immune response modulation. Through targeted degradation of specific proteins via the proteasome, the UPS ensures the timely removal of damaged, misfolded, or surplus proteins, thereby contributing to cellular health and functionality. Its intricate regulatory network and dynamic nature make the UPS a central player in cellular physiology and disease pathogenesis, warranting further investigation into its mechanisms and potential therapeutic implications [30].

The deubiquitinating enzymes (DUBs) are a crucial component of the enzyme family constituting the ubiquitin-proteasome system (UPS). DUBs play a pivotal role in maintaining protein homeostasis by cleaving ubiquitin molecules from target proteins, thereby halting their degradation and modulating their function. This process allows for the precise regulation of protein stability and activity within cells, influencing various cellular processes such as signal transduction, DNA repair, and cell cycle progression.

Interestingly, DUBs are particularly abundant in the brain and other reproductive body parts, indicating their importance in the intricate regulatory mechanisms governing neuronal function, development, and reproduction. Their localization and activity in these tissues underscore their significance in maintaining cellular integrity and functionality, highlighting the potential implications of DUB dysregulation in neurodegenerative diseases, developmental disorders, and reproductive abnormalities [31].

DUBs are often designated as Ubiquitin-specific proteases (USPs), and they encompass various types such as Ubiquitin-specific protease 1 (USP1), Ubiquitin-specific protease 7 (USP7), Ubiquitin-specific protease 11 (USP11), Ubiquitin-specific protease 22 (USP22), Ubiquitin-specific protease 44 (USP44), and Ubiquitin-specific protease 49 (USP49), which are predominantly localized within the nuclei of the cell. However, Ubiquitin-specific protease 6 (USP6) is primarily found in the plasma membrane.

The USP family of proteins plays a critical role in cancer development, contributing to various aspects of tumorigenesis including cell proliferation, survival, and metastasis. Among these, USP5, also known as Isopeptidase T, is another member of the USP family belonging to the peptidase C19 family. USP5 is involved in the cleavage of multi-ubiquitin polymers, regulating protein stability and turnover in the cell. The dysregulation of USP5 and other USP family members can lead to aberrant protein degradation pathways, contributing to the pathogenesis of cancer and other diseases [32]. The main purpose of USP5 is the reprocessing of invented polyubiquitin out at the proteasome entrance position, and stabilizing the cytosolic ubiquitin pond and it is exceedingly articulated in Gliomas [33], wherever the stabilization effect of p53 is affected due to the buildup of drifting polyubiquitin when USP5 is absent ultimately consequential in cause cell cycle arrest [34]. Exopeptidases are enzymes that hydrolyze isopeptide bonds between polyubiquitin molecules, typically from the free C-terminal end, to produce monoubiquitin. This monoubiquitin can then be salvaged and conjugated with protein substrates, playing a crucial role in protein degradation and turnover within the cell [35] .

Deubiquitinase enzymes in gliomas have been found to exhibit both anticancer and oncogenic functions. Their anticancer effects include the modulation of cancer suppressors, increased resistance to apoptosis, stabilization of oncoproteins, and maintenance of oncogenic signal transduction pathways. Additionally, deubiquitinases play a role in blocking or activating various elements of the ubiquitin-proteasome system (UPS), thereby influencing cell proliferation, apoptosis, radio/chemoresistance development, modulation of the tumor microenvironment, and maintenance of glioma stem cell (GSC) stemness, which encompasses the capacity for self-renewal and multipotentiality [36, 37].

Some studies show that deubiquitinase enzymes contribute to cell differentiation processes and Epithelial-to-

[DOI: 10.61186/ijbc.16.2.70]

mesenchymal transition (EMT) [38]. Mechanisms of action, and effects of deubiquitinases in gliomas are provided in **Table 1.**

4.2. Competing Polyadenylation

The mechanism of RNA processing, such as Alternative Polyadenylation, results in the generation of 3' termini on mRNAs and RNA polymerase II transcripts. According to Tian and Manley, this process is a major mechanism of gene regulation, as it is widespread across all eukaryotic species. Maturation of mRNA transcripts necessitates cleavage and polyadenylation. Following the polyadenylation signal AAUAAA, an untemplated poly(A) tract is added. The pre-mRNA is then cleaved at approximately 10-30 nucleotides downstream[57, 58] Lan and Zhang said Shortening of 3′ untranslated regions (3' UTR) mediated by Alternative polyadenylation (APA) has direct oncogenic effects which promote tumorigenesis in gliomas [59]. Additional research demonstrates that RBPs have an impact on target mRNAs, influencing the polyadenylation and cleavage patterns of these mRNA sites. RBPs can either compete with or enhance the binding site of polyadenylation machinery proteins, thereby modulating the processing of target mRNAs [60].

The polyadenylation process is orchestrated by a polymeric protein complex comprising four subunits: a division and polyadenylation-specific factor known as Cleavage and Polyadenylation Specific Factor (CPSF), a cleavage stimulation factor termed Cleavage Stimulation Factor (CstF), mammalian cleavage factor I (CFIm), and mammalian cleavage factor II (CFIIm) [61]. Assembly of CPSF with CstF and cleavage factor I (CFI) help ensure the binding and accurate positioning efficiency of the overall complex [62]. According to Masamha, Xia et al., the downregulation of CFIm25 results in the enhancement of tumorigenic properties and an increase in tumor size in glioblastoma. Conversely, the overexpression of CFIm25 leads to a reduction in these properties and inhibits tumor growth.[63] Another study highlights the role of CFIm25 expression in glioma cell proliferation. Various investigations have demonstrated that CFIm25 expression induces glioma cell proliferation by modulating the NF-kB signaling pathway. Subsequent research indicates that a downstream target for CFIm25 regulation is the NF-kB inhibitor zeta (NFKBIZ) [64].

Sun, Li et al. observed that low expression of CFIm25 corresponded with shorter 3' UTRs in glioblastoma multiforme (GBM) cell lines. Upon artificially increasing CFIm25 expression, there was a subsequent lengthening of the 3' UTR, leading to inhibition of tumor growth and cell proliferation. Conversely, high CFIm25 expression in GBM cell lines resulted in shortened 3' UTRs, promoting tumor growth and cell proliferation upon reduced CFIm25 expression. Further investigations underscored the significant role of CFIm25 in human brain gliomas, operating through an NF-Kb-dependent pathway to facilitate glioma cell proliferation [65].

4.3. Translational regulation

In translational regulation ,RBPs plays a substantial role on the mechanism and impact of cancer development, regulation, progression, and response to therapy remain to be fully understood. [66] The translation process is significantly regulated by hnRNP H/F RBPs, which employ various mechanisms to modulate the expression and activity of translation initiation factors. Among these mechanisms, hnRNP H/F have been observed to regulate the phosphorylation of eIF4E and its translational targets, thereby influencing RNA splicing of A-Raf kinase mRNA. This regulation, in turn, impacts signaling pathways such as MEK-ERK/MAPK. Additionally, the modulation of RNA G-quadruplex (RG4s), which are RNA structures, has been found to mimic the translation regulation mediated by hnRNP H/F in GBM cells [67].

To control gene expression, mRNAs interact at translational level with RBPs in three phases: initiation, elongation, and termination. The mRNA molecules on both 5' and 3' UTR region binding sites for RBPs are present.[68] In translation, the RNA-binding protein Musashi (MSI) plays a crucial role. Musashi comprises two members, MSI1 and MSI2, which are instrumental in regulating hematopoietic stem cells and serve as regulators of biological processes associated with cancer initiation, progression, and drug resistance. Studies have shown that MSI is closely associated with various cancer types, including glioblastoma and breast cancer [69].

In the communication process, flow of information that coordinates all biological activities within a cell, intracellular signaling pathway also plays important role [70]. A critical signaling pathway in glioma oncogenicity involves the activation of Receptor Tyrosine Kinases (RTKs). The amplification of glioma was initially identified in the 1980s, and from the early stages of glioma research, the involvement of RTKs has been emphasized. RTKs bind to specific ligands in the extracellular ligand-binding domain, leading to self-dimerization in the plasma membrane, which in turn triggers autophosphorylation [71].

[DOI: 10.61186/ijbc.16.2.70]

Table 1. Deubiquitine enzymes involved in suppression and exacerbation.

Deubiquitinase	Mechanism of action	Effects	Reference
Tumor promoter deubiquitinases			
HAUSP	• They exhibit elevated expression levels in gliomas. • They are involved in stabilizing LSD1, MDM2, and NANIG.	Decrease the survival rate of patients and impair the p53 signaling pathway. Increase the proliferation, invasion, and stemness of glioma cells.	[39]
OTUB1	• Upregulation observed in glioblastoma multiforme. • Facilitates the stabilization of Vimentin and Snail.	Reduce survival rates and enhance migration and epithelial-to-mesenchymal transition (EMT).	[40]
USP1	• Overexpression detected in glioblastoma multiforme. • USP1 stabilizes ID1, ID2, and CHEK1. • Regulates the response to damaged DNA and maintains stem cells. • Stabilizes EZH2, a transcriptional repressor, in anti-tumor protein.	Enhance the survival rate and growth of Glioblastoma stem cells, elevate radio resistance of Glioblastoma multiforme, and promote the survival of proneural glioma cells as well as the proliferation of glioma cells.	[41]
USP3	• Overexpression in glioblastoma multiforme and • Stabilize Snail • It is transcription factor that promote EMT	Patient survival rates decrease while invasion, migration, and tumor growth increase.	[42]
USP4	• Overexpression in Glioblastoma multiforme. • Stabilize PCNA, Bcl-2, p-ERK1/2, and modulate TGF-β.	Patient survival rate decreases while proliferation and resistance to TMZ and the ERK pathway increase. Additionally, there is a decrease in p53-dependent apoptosis.	[43]
USP5	• In glioblastoma multiforme, an abnormal splicing event happens that generate an oncogenic isoform of USP5.	Tumorigenicity increases.	[36]
USP8	• Antiapoptotic protein FLIP stabilize with the help of USP8	Increase GBM resistance.	[36]
USP9X	• It prevents β-catenin degradation, which promotes the expression of c-MYC and cyclin D1. Additionally, it stabilizes ALDH1A3.	The Wnt/β-catenin signaling pathway is enhanced, leading to increased proliferation, survival, tumorigenicity, and self-renewal of GSCs.	[44, 45]
USP10	• Upregulation in GBM. • Unknown mode of action	Decrease patient survival rate	[36]
USP13	• Averts c-MYC ubiquitination which induced by the ligase FBXL14.	Increase GSC self-renewal and tumorigenic probability	[46]
USP22	• Increased manifestation in glioma samples. • Stabilize of CDK1, CDK2, cyclin KDM1, B1, and BMI1	There is an increase in proliferation, migration, survival, and invasion of glioma cells, promoting tumorigenesis and stem cell self-renewal. This ultimately leads to a decrease in patient survival rate.	[47]
USP28	• Over modulation in glioma. • Stabilization of the oncoprotein c-MYC.	Decrease patient Survival rate and increase Proliferation and tumorigenicity.	[48]
UPS39	• Upregulation in glioma. • Stabilize oncoprotein TAZ and securing	Increase migration, invasion and proliferation.	[49]
USP44	• Modulation in GBM • Stabilize Securin oncoprotein	There is an increase in tumorigenesis, proliferation, invasion, and migration, accompanied by a decrease in patient survival rate and apoptosis.	[50]

[DOI: 10.61186/ijbc.16.2.70]

USP48	• Its presence is correlated with the malignancy of glioma, stabilizing Gli1 and sequentially activating the Hedgehog signaling pathway.	Increase tumorigenicity and Proliferation	[51]
Tumor suppressor deubiquitinase			
USP2a	• Overexpression is observed in tissues associated with glioma development, with levels correlating with increased tumor histological grade, and it stabilizes levels of the pro-apoptotic protein Mdm4.	Escalation of p53-dependent intrinsic apoptosis in Glioblastoma multiforme.	[36, 52]
USP11	• Averts the ubiquitination and proteasomal deprivation of the PML protein, a vital constituent of nuclear structures.	There is a decrease in proliferation, invasion, and tumor growth, as well as a reduction in the tumor-forming ability. Moreover, there is a decrease in self-renewal and therapeutic resistance of glioma stem cells.	[53]
USP17	• Downregulation in glioma. • Countenance inversely correlated with glioma histological grade. • Level of RAS and MYC protein reduce	Decrease proliferation and Tumorigenesis	[54]
USP26	• SMAD7 stabilize with USP2	Decrease TGF-β signaling and Increase patients Survival rate.	[55]
Deuibiquitinase with twofold role			
USP15	• Conflicting evidence exists. • USP15 expression is elevated or diminished in specific subgroups of Glioblastoma multiforme. • USP15 exhibits an anticancer function by deubiquitinating TGF-βR1, thereby inhibiting the activity of the ligase complex SMURF2. • It demonstrates an anticancer effect by stabilizing HECTD1, the ligase.	There is an increase in TGF-β signaling and tumorigenicity, proliferation, and invasion. Conversely, there is a decrease in Wnt signaling, which typically exhibits anticancer properties.	[56]

4.4. Intracellular signal disruption

To regulate the progression of glioma via the Notch signaling pathway, several miRNAs known to be associated with gliomas, such as miRNA-129, miRNA-34 family, and miRNA-326, have been identified. Research indicates that glioma cell recurrence and active angiogenesis, key factors in glioma development, are regulated by various factors, including Notch signaling [72].

Transforming growth factor-beta (TGF-β) plays a significant role in regulating the proliferation and apoptosis of various cells, including glioma cells. According to Kaminska and Cyranowski, TGF-β-activated kinase-1 (TAK1) is a crucial component of the TGF-β signaling pathway, activating mitogen-activated protein kinase (MAPK) cascades. Negative regulation of TGF-β/Smad signaling may occur through inhibitory Smad 6/7. Genetic alterations related to TGF-β in gliomas are rare.[73] TGFb plays a dual role in cancer; firstly, studies show that at early stages of carcinogenesis, TGFb performs the functions as a tumour suppressor, while in advanced stages, it promotes cellular metastasis through the EMT process [74].

5. RBP METHYLATION ACTIVATES ONCOGENIC PATHWAYS

RBPs are important proteins that regulate various cellular processes such as RNA metabolism, splicing, and translation.[75] Methylation is a chemical modification that can occur on RBPs where a methyl group is added to the protein.[76] RBP methylation can change the function and stability of the protein and its interactions with other molecules in the cell. [77] Understanding RBP methylation is important to understand how it may contribute to cancer development.

Research by M. Liu explored the involvement of three proteins—BUD13, Cyclin-dependent kinase 12 (CDK12), and Muscleblind-like splicing regulator 1 (MBNL1)—in glioblastoma (GBM). Their study revealed elevated levels of BUD13 and CDK12, alongside decreased levels of MBNL1 in GBM cells and tissues. Manipulating the expression of these proteins resulted in alterations in the formation of vascular mimicry (VM), a process crucial in GBM progression. The findings underscore the

[DOI: 10.61186/ijbc.16.2.70]

significance of the BUD13/CDK12/MBNL1 axis in VM formation and propose these proteins as potential therapeutic targets for GBM treatment. [78] Alterations in the methylation status of RBPs can trigger oncogenic signaling pathways, culminating in unregulated cell proliferation and invasion. One such RBP, Fox-1 homolog 1 (RBFOX1), acts as a tumor suppressor gene by exerting control over cell growth. However, when RBFOX1 undergoes methylation, its tumor-suppressive function is compromised, paving the way for tumorigenesis. In gliomas, a specific type of brain tumor, RBFOX1 is susceptible to methylation-induced damage. Methylation induces a chemical modification that effectively silences genes, including RBFOX1. Consequently, the impaired function of methylated RBFOX1 promotes the unchecked growth of glioma tumors, highlighting the critical role of RBP methylation in glioma pathogenesis.[79]

The methylation of RBPs can facilitate cancer development through various mechanisms. One significant pathway involves altering the expression or activity of critical proteins that regulate fundamental cellular processes such as the cell cycle, DNA repair, and apoptosis. For example, Serine/arginine-rich splicing factor 3 (SRSF3) is an essential protein involved in RNA splicing, a process crucial for generating functional proteins. However, when SRSF3 undergoes methylation, it disrupts normal RNA splicing, leading to the aberrant production of proteins that drive cell growth and proliferation. Additionally, methylated SRSF3 can suppress programmed cell death, allowing cancer cells to evade apoptosis, and impair the immune system's ability to recognize and eliminate cancerous cells. These dysregulated processes likely contribute to the development and progression of aggressive cancers like glioblastoma, underscoring the significance of RBP methylation in tumorigenesis. [80]

Knowing how RBP methylation contributes to cancer can significantly impact the clinical field. RBP methylation can diagnose cancer and predict the prognosis [81]. Additionally, targeting RBP methylation pathways could be a new way to treat cancer as researchers have developed small molecule inhibitors that target Oncogenic pathways, and early studies have shown they can prevent cancer growth and spread. [82]

6. DIFFERENTIALLY EXPRESSED GENES DURING GLIOMA PROGRESSION

Glioma progression is the term used to describe the worsening of tumours that originate from glial cells in the brain [87], accounting for the majority of malignant brain tumors. The process involves the tumors becoming more aggressive and invasive,[83] resulting in negative outcomes for patients. To comprehend the molecular mechanisms that underlie glioma progression, it is crucial to understand gene expression, which is the process by which genetic information produces proteins, the fundamental components of cells.

Differentially expressed genes play an important role in the progression of glioma. Differential gene expression analysis is a common method for determining either upregulated or downregulated genes during glioma progression compared to normal brain tissue. This analysis can be conducted using various techniques, including microarray analysis [84] and RNA sequencing. Tao et al. used microarray analysis to measure the levels of EMT-related genes in gliomas, a type of brain tumour. They discovered that 22 of these genes were differentially expressed in two groups of gliomas. The researchers then used a statistical method called Cox regression to analyze how the expression of EMT-related genes was related to patient survival. They found that patients with higher levels of EMT-related genes in their gliomas had a shorter survival time than patients with lower levels of these genes. [85]

Yao Jiang et al. conducted a study and the purpose of this research was to determine which genes are involved in the advancement and outlook of low-grade gliomas (LGG) to high-grade gliomas (HGG). By studying the genes of both LGG and HGG, the scientists found 74 genes expressed differently, mainly related to the extracellular matrix, focal adhesion, and PI3K-Akt signaling pathway. Among these genes, six were identified as "crosstalk genes," including COL1A1, COL1A2, COL3A1, COL4A1, COL4A2, and COL5A2, and related to a low survival rate in LGG patients. The researchers believe these crosstalk genes play a role in the progression and prognosis of LGG via the extracellular matrix (ECM)-receptor interaction pathway. [86] Several studies have been conducted to identify differentially expressed genes associated with glioma progression, with one study revealing that the gene Epidermal growth factor receptor (EGFR) demonstrated much higher expression levels in gliomas than in normal brain tissue. Furthermore, high levels of EGFR expression were linked to unfavorable outcomes in patients [87].

The clinical implications of understanding the role of differentially expressed genes in glioma progression are significant, as they can facilitate the development of new therapies and prognostic tools. For example, drugs that target the EGFR signaling pathway have been developed to treat gliomas with high EGFR expression.

[DOI: 10.61186/ijbc.16.2.70]

7. CIRCULAR RNA AND RBP INTERACTION

Circular RNA (circRNA) is a special type of RNA that forms a closed-loop structure. It is made when a part of the RNA is spliced to create a circle instead of a straight line.**[88]** CircRNAs are very stable and can affect how genes are expressed by interacting with RBPs or soaking up small RNA molecules called miRNAs.**[89]** RBPs are proteins that interact with RNA molecules to control how they work. They help regulate how genes are expressed after they are transcribed from DNA. Some RBPs interact with circRNAs and affect how they function. This interaction can also affect the behavior of RBPs, influencing various biological processes **[90]**.

Exploring the intricate interplay between circular RNAs (circRNAs) and RNA-binding proteins (RBPs) holds significant promise for unraveling key biological processes and diseases. This dynamic interaction between circRNAs and RBPs exerts profound effects on gene expression regulation, with implications for various pathological conditions, including glioma, a formidable form of brain cancer.

For instance, investigations into the role of circRNAs have shed light on their involvement in glioma tumorigenesis. Notably, Circ-SHPRH has emerged as a pivotal player in this context. Studies have revealed that Circ-SHPRH harbors an internal ribosome entry site (IRES)-driven open reading frame (ORF), enabling its translation into a functional protein. Interestingly, this protein is expressed in normal human brains and functions to suppress glioma tumorigenesis, underscoring the intricate regulatory mechanisms mediated by circRNAs in cancer biology **[91]**. Circ-HIPK3 sponges miR-654 and promotes IGF2BP3 expression, activating the IGF2/PI3K/Akt signaling pathway and promoting glioma cell proliferation, invasion, and tumour propagation **[92]**. Circ-SHKBP1 sponges miR-544a/miR-379 and up-regulates FOXP1/FOXP2, activating the PI3K/Akt pathway and inducing angiogenic processes in GBM **[93]**. Hsa_circ_0000177 targets miR-638 to increase FZD7 expression and activate the Wnt signaling pathway, promoting glioma cell proliferation and invasion **[94]**.

Understanding how circRNAs and RBPs interact in glioma and other diseases can lead to new treatments. Targeting circRNAs or RBPs involved in disease progression could be a new therapeutic approach. Additional research is needed to identify new circRNAs and RBPs involved in disease and to understand how they interact. This research could lead to new therapies and a better knowledge of disease at the molecular level.

8. CONCLUSION

RBP dynamics are important in glioma molecular pathways, contributing to tumour development, progression, and therapeutic resistance. The emerging evidence suggests that RBPs hold immense potential as therapeutic and diagnostic biomarker targets in glioma management. Identifying RBP-Targeted Therapeutic Strategies opens opportunities for developing targeted therapeutic strategies in future.

Conflict of interest

There is nothing to declare.

Acknowledgements:

We would like to express our sincere gratitude to Mr. Junaid Iqbal and Ms. Aghna Maryam for their invaluable support and assistance in writing this review. Their expertise and dedication greatly contributed to the quality and depth of the content. We are truly appreciative of their collaboration and contributions to this work.

References

1. Wang, Z., et al., Integrated analysis of RNA-binding proteins in glioma. Cancers, 2020. 12(4): p. 892.
2. Kang, D., Y. Lee, and J.-S. Lee, RNA-binding proteins in cancer: functional and therapeutic perspectives. Cancers, 2020. 12(9): p. 2699.
3. Corley, M., M.C. Burns, and G.W. Yeo, How RNA-binding proteins interact with RNA: molecules and mechanisms. Molecular cell, 2020. 78(1): p. 9-29.
4. Emmanouilidis, L., et al., Structural biology of RNA-binding proteins in the context of phase separation: What NMR and EPR can bring? Current Opinion in Structural Biology, 2021. 70: p. 132-138.
5. Yan, J., et al., Delivery of CRISPR-Cas9 system for screening and editing RNA binding proteins in cancer. Advanced Drug Delivery Reviews, 2022. 180: p. 114042.
6. Goenka, A., et al., The role of non-coding RNAs in glioma. Biomedicines, 2022. 10(8): p. 2031.
7. Luo, X., et al., A Novel Immune Gene-Related Prognostic Score Predicts Survival and Immunotherapy Response in Glioma. Medicina, 2022. 59(1): p. 23.
8. He, Z., et al., miR-1297 sensitizes glioma cells to temozolomide (TMZ) treatment through targeting adrenomedullin (ADM). Journal of translational medicine, 2022. 20(1): p. 1-14.
9. Wank, M., et al., Human glioma migration and infiltration properties as a target for personalized radiation medicine. Cancers, 2018. 10(11): p. 456.
10. Kosti, A., et al., The RNA-binding protein SERBP1 functions as a novel oncogenic factor in glioblastoma by bridging cancer

[DOI: 10.61186/ijbc.16.2.70]

metabolism and epigenetic regulation. Genome biology, 2020. 21(1): p. 1-32.
11. Jiang, M.-P., et al., The emerging role of the interactions between circular RNAs and RNA-binding proteins in common human cancers. Journal of Cancer, 2021. 12(17): p. 5206.
12. Nabors, L.B., et al., Tumor necrosis factor α induces angiogenic factor up-regulation in malignant glioma cells: a role for RNA stabilization and HuR. Cancer research, 2003. 63(14): p. 4181-4187.
13. Bell, J.L., et al., Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression? Cellular and molecular life sciences, 2013. 70: p. 2657-2675.
14. Yang, Y., et al., Dynamic transcriptomic m6A decoration: writers, erasers, readers and functions in RNA metabolism. Cell research, 2018. 28(6): p. 616-624.
15. Viswanathan, S.R., G.Q. Daley, and R.I. Gregory, Selective blockade of microRNA processing by Lin28. Science, 2008. 320(5872): p. 97-100.
16. Duan, J., et al., Upregulation of far upstream element-binding protein 1 (FUBP1) promotes tumor proliferation and tumorigenesis of clear cell renal cell carcinoma. PLoS One, 2017. 12(1): p. e0169852.
17. Afonso-Grunz, F. and S. Müller, Principles of miRNA–mRNA interactions: beyond sequence complementarity. Cellular and Molecular Life Sciences, 2015. 72: p. 3127-3141.
18. Li, A., et al., Cytoplasmic m6A reader YTHDF3 promotes mRNA translation. Cell research, 2017. 27(3): p. 444-447.
19. Bettegowda, C., et al., Mutations in CIC and FUBP1 contribute to human oligodendroglioma. Science, 2011. 333(6048): p. 1453-1455.
20. Kudinov, A.E., et al., Musashi RNA-binding proteins as cancer drivers and novel therapeutic targets. Clinical Cancer Research, 2017. 23(9): p. 2143-2153.
21. Chen, Y., et al., Biallelic variants in RBM42 cause a multisystem disorder with neurological, facial, cardiac, and musculoskeletal involvement. Protein & Cell, 2024. 15(1): p. 52-68.
22. Wang, Q., et al., Identification of KIF15 as a potential therapeutic target and prognostic factor for glioma. Oncology Reports, 2020. 43(4): p. 1035-1044.
23. Chen, Y., Y.-H. Tsai, and S.-H. Tseng, Regulation of the expression of cytoplasmic polyadenylation element binding proteins for the treatment of cancer. Anticancer Research, 2016. 36(11): p. 5673-5680.
24. Liao, J., et al., Insight into the structure, physiological function, and role in cancer of m6A readers—YTH domain-containing proteins. Cell Death Discovery, 2022. 8(1): p. 137.
25. Velasco, M.X., et al., The diverse roles of RNA-binding proteins in glioma development. The mRNA Metabolism in Human Disease, 2019: p. 29-39.
26. Wang, X., et al., The circACTN4 interacts with FUBP1 to promote tumorigenesis and progression of breast cancer by regulating the expression of proto-oncogene MYC. Molecular Cancer, 2021. 20(1): p. 1-21.
27. Li, Z., et al., The RNA-binding motif protein family in cancer: friend or foe? Frontiers in oncology, 2021. 11: p. 757135.
28. Narayanan, S., et al., Targeting the ubiquitin-proteasome pathway to overcome anti-cancer drug resistance. Drug Resistance Updates, 2020. 48: p. 100663.
29. Vashistha, V., et al., Depleting deubiquitinating enzymes promotes apoptosis in glioma cell line via RNA binding proteins SF2/ASF1. Biochemistry and Biophysics Reports, 2020. 24: p. 100846.
30. Jin, W.L., X.Y. Mao, and G.Z. Qiu, Targeting deubiquitinating enzymes in glioblastoma multiforme: expectations and challenges. Medicinal Research Reviews, 2017. 37(3): p. 627-661.
31. Jeong, M., et al., USP8 suppresses death receptor-mediated apoptosis by enhancing FLIPL stability. Oncogene, 2017. 36(4): p. 458-470.
32. Dayal, S., et al., Suppression of the deubiquitinating enzyme USP5 causes the accumulation of unanchored polyubiquitin and the activation of p53. Journal of Biological Chemistry, 2009. 284(8): p. 5030-5041.
33. Liu, Y., et al., Ubiquitin specific peptidase 5 mediates Histidine-rich protein Hpn induced cell apoptosis in hepatocellular carcinoma through P14-P53 signaling. Proteomics, 2017. 17(12): p. 1600350.
34. Maksoud, S., The role of the ubiquitin proteasome system in glioma: Analysis emphasizing the main molecular players and therapeutic strategies identified in glioblastoma multiforme. Molecular neurobiology, 2021. 58(7): p. 3252-3269.
35. Lee, J.-K., et al., USP1 targeting impedes GBM growth by inhibiting stem cell maintenance and radioresistance. Neuro-oncology, 2015. 18(1): p. 37-47.
36. Suresh, B., et al., Regulation of pluripotency and differentiation by deubiquitinating enzymes. Cell Death & Differentiation, 2016. 23(8): p. 1257-1264.
37. Cheng, C.-d., et al., HAUSP promoted the growth of glioma cells in vitro and in vivo via stabilizing NANOG. Pathology-Research and Practice, 2020. 216(4): p. 152883.
38. Yi, L., et al., Stabilization of LSD1 by deubiquitinating enzyme USP7 promotes glioblastoma cell tumorigenesis and metastasis through suppression of the p53 signaling pathway. Oncology reports, 2016. 36(5): p. 2935-2945.
39. Xu, L., et al., Silencing of OTUB1 inhibits migration of human glioma cells in vitro. Neuropathology, 2017. 37(3): p. 217-226.
40. Ma, L., et al., Aberrant activation of β-catenin signaling drives glioma tumorigenesis via USP1-mediated stabilization of EZH2. Cancer research, 2019. 79(1): p. 72-85.
41. Rahme, G.J., et al., PDGF Engages an E2F-USP1 Signaling Pathway to Support ID2-Mediated Survival of Proneural Glioma CellsA PDGF-E2F-USP1-ID2 Axis Is Required for Proneural Glioma. Cancer research, 2016. 76(10): p. 2964-2976.
42. Fan, L., et al., Ubiquitin-specific protease 3 promotes glioblastoma cell invasion and epithelial–mesenchymal transition via stabilizing Snail. Molecular Cancer Research, 2019. 17(10): p. 1975-1984.
43. Zhou, Y., et al., Ubiquitin-specific protease 4 promotes glioblastoma multiforme via activating ERK pathway. OncoTargets and therapy, 2019. 12: p. 1825.

[DOI: 10.61186/ijbc.16.2.70]

44. Qin, N., et al., Deubiquitinating enzyme 4 facilitates chemoresistance in glioblastoma by inhibiting P53 activity. Oncology Letters, 2019. 17(1): p. 958-964.
45. Chen, Z., et al., USP9X deubiquitinates ALDH1A3 and maintains mesenchymal identity in glioblastoma stem cells. The Journal of Clinical Investigation, 2019. 129(5): p. 2043-2055.
46. Yang, B., et al., Deubiquitinase USP9X deubiquitinates β-catenin and promotes high grade glioma cell growth. Oncotarget, 2016. 7(48): p. 79515.
47. Fang, X., et al., Deubiquitinase USP13 maintains glioblastoma stem cells by antagonizing FBXL14-mediated Myc ubiquitination. Journal of Experimental Medicine, 2017. 214(1): p. 245-267.
48. Qiu, G.Z., et al., Ubiquitin-specific protease 22 acts as an oncoprotein to maintain glioma malignancy through deubiquitinating B cell-specific Moloney murine leukemia virus integration site 1 for stabilization. Cancer Science, 2018. 109(7): p. 2199-2210.
49. Liang, J., et al., Ubiquitin-specific protease 22 promotes the proliferation, migration and invasion of glioma cells. Cancer Biomarkers, 2018. 23(3): p. 381-389.
50. Zhou, A., et al., Nuclear GSK3β promotes tumorigenesis by phosphorylating KDM1A and inducing its deubiquitylation by USP22. Nature cell biology, 2016. 18(9): p. 954-966.
51. Wang, Z., et al., Ubiquitin-specific protease 28 is overexpressed in human glioblastomas and contributes to glioma tumorigenicity by regulating MYC expression. Experimental Biology and Medicine, 2016. 241(3): p. 255-264.
52. Ding, K., et al., RNA splicing factor USP39 promotes glioma progression by inducing TAZ mRNA maturation. Oncogene, 2019. 38(37): p. 6414-6428.
53. Zou, Y., et al., Overexpression of ubiquitin specific proteases 44 promotes the malignancy of glioma by stabilizing tumor-promoter securin. Oncotarget, 2017. 8(35): p. 58231.
54. Zhou, A., et al., Gli1-induced deubiquitinase USP 48 aids glioblastoma tumorigenesis by stabilizing Gli1. EMBO reports, 2017. 18(8): p. 1318-1330.
55. Boustani, M.R., et al., Overexpression of ubiquitin-specific protease 2a (USP2a) and nuclear factor erythroid 2-related factor 2 (Nrf2) in human gliomas. Journal of the neurological sciences, 2016. 363: p. 249-252.
56. Wu, H.-C., et al., USP11 regulates PML stability to control Notch-induced malignancy in brain tumours. Nature communications, 2014. 5(1): p. 3214.
57. Hu, M., et al., Expression and functional implications of USP17 in glioma. Neuroscience Letters, 2016. 616: p. 125-131.
58. Kit Leng Lui, S., et al., USP 26 regulates TGF-β signaling by deubiquitinating and stabilizing SMAD 7. EMBO reports, 2017. 18(5): p. 797-808.
59. Xu, K., et al., Ubiquitin-specific protease 15 promotes tumor cell invasion and proliferation in glioblastoma. Oncology Letters, 2018. 15(3): p. 3846-3851.
60. Oikonomaki, M., P. Bady, and M.E. Hegi, Ubiquitin Specific Peptidase 15 (USP15) suppresses glioblastoma cell growth via stabilization of HECTD1 E3 ligase attenuating WNT pathway activity. Oncotarget, 2017. 8(66): p. 110490.
61. Tian, B. and J.L. Manley, Alternative polyadenylation of mRNA precursors. Nature reviews Molecular cell biology, 2017. 18(1): p. 18-30.
62. Mayr, C. and D.P. Bartel, Widespread shortening of 3′ UTRs by alternative cleavage and polyadenylation activates oncogenes in cancer cells. Cell, 2009. 138(4): p. 673-684.
63. Lan, Y.-L. and J. Zhang, Modulation of untranslated region alternative polyadenylation in glioma tumorigenesis. Biomedicine & Pharmacotherapy, 2021. 137: p. 111416.
64. Erson-Bensan, A.E. and T. Can, Alternative Polyadenylation: Another Foe in CancerAPA in Cancer. Molecular Cancer Research, 2016. 14(6): p. 507-517.
65. Chu, Y., et al., Nudt21 regulates the alternative polyadenylation of Pak1 and is predictive in the prognosis of glioblastoma patients. Oncogene, 2019. 38(21): p. 4154-4168.
66. Chatrikhi, R., et al., RNA binding protein CELF2 regulates signal-induced alternative polyadenylation by competing with enhancers of the polyadenylation machinery. Cell reports, 2019. 28(11): p. 2795-2806. e3.
67. Masamha, C.P., et al., CFIm25 links alternative polyadenylation to glioblastoma tumour suppression. Nature, 2014. 510(7505): p. 412-416.
68. Lou, J.-C., et al., Silencing NUDT21 attenuates the mesenchymal identity of glioblastoma cells via the NF-κB pathway. Frontiers in molecular neuroscience, 2017. 10: p. 420.
69. Sun, X., et al., CFIm25 in Solid Tumors: Current Research Progress. Technology in Cancer Research & Treatment, 2020. 19: p. 1533033820933969.
70. Le Bras, M., et al., Translational Regulation by hnRNP H/F Is Essential for the Proliferation and Survival of Glioblastoma. Cancers, 2022. 14(5): p. 1283.
71. Herviou, P., et al., hnRNP H/F drive RNA G-quadruplex-mediated translation linked to genomic instability and therapy resistance in glioblastoma. Nature communications, 2020. 11(1): p. 2661.
72. Moore, K.S. and M. von Lindern, RNA binding proteins and regulation of mRNA translation in erythropoiesis. Frontiers in physiology, 2018. 9: p. 910.
73. Kudinov, A.E., et al., Musashi RNA-Binding Proteins as Cancer Drivers and Novel Therapeutic TargetsMusashi Proteins as Cancer Drivers and Therapeutic Targets. Clinical Cancer Research, 2017. 23(9): p. 2143-2153.
74. Kanthasamy, A., et al., Disruption of intracellular signaling, in An Introduction to Interdisciplinary Toxicology. 2020, Elsevier. p. 81-96.
75. Tomiyama, A. and K. Ichimura. Signal transduction pathways and resistance to targeted therapies in glioma. in Seminars in cancer biology. 2019. Elsevier.
76. Yan, D., et al., Molecular mechanism of Notch signaling with special emphasis on microRNAs: Implications for glioma. Journal of cellular physiology, 2019. 234(1): p. 158-170.
77. Kaminska, B. and S. Cyranowski, Recent advances in understanding mechanisms of TGF beta signaling and its role in glioma pathogenesis. Glioma Signaling, 2020: p. 179-201.
78. Janakiraman, H., et al., The Long (lncRNA) and Short (miRNA) of It: TGFβ-Mediated Control of RNA-Binding Proteins

[DOI: 10.61186/ijbc.16.2.70]

and Noncoding RNAsTGFβ-Mediated Posttranscriptional Gene Regulation in Cancer. Molecular Cancer Research, 2018. 16(4): p. 567-579.
79. Mehta, M., et al., RNA binding proteins (RBPs) and their role in DNA damage and radiation response in cancer. Advanced Drug Delivery Reviews, 2022: p. 114569.
80. He, P.C. and C. He, m6A RNA methylation: from mechanisms to therapeutic potential. The EMBO journal, 2021. 40(3): p. e105977.
81. He, Q., et al., The underlying molecular mechanisms and prognostic factors of RNA binding protein in colorectal cancer: a study based on multiple online databases. Cancer Cell International, 2021. 21(1): p. 1-16.
82. Liu, M., et al., The mechanism of BUD13 m6A methylation mediated MBNL1-phosphorylation by CDK12 regulating the vasculogenic mimicry in glioblastoma cells. Cell Death & Disease, 2022. 13(12): p. 1017.
83. Lin, J.-C., et al., Genome-Wide Association Study Identifies Multiple Susceptibility Loci for Malignant Neoplasms of the Brain in Taiwan. Journal of Personalized Medicine, 2022. 12(7): p. 1161.
84. Song, X., et al., SRSF3-regulated RNA alternative splicing promotes glioblastoma tumorigenicity by affecting multiple cellular processes. Cancer research, 2019. 79(20): p. 5288-5301.
85. Cao, L., et al., Development and validation of an RBP gene signature for prognosis prediction in colorectal cancer based on WGCNA. Hereditas, 2023. 160(1): p. 1-19.
86. Fattahi, S., et al., PI3K/AKT/mTOR signaling in gastric cancer: Epigenetics and beyond. Life sciences, 2020. 262: p. 118513.
87. Kolostova, K., et al., Next generation sequencing of glioblastoma circulating tumor cells: non-invasive solution for disease monitoring. American Journal of Translational Research, 2021. 13(5): p. 4489.
88. Li, X. and H. Diao, Circular RNA circ_0001946 acts as a competing endogenous RNA to inhibit glioblastoma progression by modulating miR-671-5p and CDR1. Journal of cellular physiology, 2019. 234(8): p. 13807-13819.
89. Tao, C., et al., Genomics and prognosis analysis of epithelial-mesenchymal transition in glioma. Frontiers in Oncology, 2020. 10: p. 183.
90. Jiang, Y., et al., Identification of genes related to low-grade glioma progression and prognosis based on integrated transcriptome analysis. Journal of cellular biochemistry, 2020. 121(5-6): p. 3099-3111.
91. Hao, Z. and D. Guo, EGFR mutation: novel prognostic factor associated with immune infiltration in lower-grade glioma; an exploratory study. BMC cancer, 2019. 19(1): p. 1-13.
92. Li, J., et al., Circular RNAs in cancer: biogenesis, function, and clinical significance. Trends in cancer, 2020. 6(4): p. 319-336.
93. Verduci, L., et al., CircRNAs: role in human diseases and potential use as biomarkers. Cell death & disease, 2021. 12(5): p. 468.
94. Zang, J., D. Lu, and A. Xu, The interaction of circRNAs and RNA binding proteins: an important part of circRNA maintenance and function. Journal of neuroscience research, 2020. 98(1): p. 87-97.
95. Zhang, M., et al., A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. Oncogene, 2018. 37(13): p. 1805-1814.
96. Jin, P., et al., CircRNA circHIPK3 serves as a prognostic marker to promote glioma progression by regulating miR-654/IGF2BP3 signaling. Biochemical and biophysical research communications, 2018. 503(3): p. 1570-1574.
97. He, Q., et al., circ-SHKBP1 regulates the angiogenesis of U87 glioma-exposed endothelial cells through miR-544a/FOXP1 and miR-379/FOXP2 pathways. Molecular Therapy-Nucleic Acids, 2018. 10: p. 331-348.
98. Chen, Z. and X. Duan, hsa_circ_0000177-miR-638-FZD7-Wnt signaling cascade contributes to the malignant behaviors in glioma. DNA and cell biology, 2018. 37(9): p. 791-797.

[DOI: 10.61186/ijbc.16.2.70]