International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 9, No. 2, 2025

Research Progress on TRIM28 and GBM

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Abstract: Glioblastoma (GBM) is the most aggressive and deadly malignant glioma of the adult central nervous system (CNS), making the discovery of related genes essential for its treatment and prognosis. Recent study has shown that Tripartite motif (TRIM) is involved in several biological processes, both suppressing tumor formation and facilitating tumor growth and invasion. It may modulate the onset and progression of cancers via many methods. tripartite motif-containing protein 28 (TRIM28) is a member of the TRIM protein family, serving as a multifunctional transcriptional regulator that participates in chromatin remodeling, DNA damage repair, and the maintenance of stem cell pluripotency. Recent research indicates that TRIM28 influences the self-renewal and chemotherapy resistance of tumor stem cells via modulating the expression of tumor stem cell markers, including Prominin-1 (CD133) in GBM. Research demonstrates that TRIM28 directly engages with the promoter region of the CD133 gene via an epigenetic mechanism, inhibits histone acetylation (particularly h3k27ac), and therefore downregulates CD133 expression. The knockdown of trim28 might significantly reduce the stem cell properties of GBM cells, hinder tumor sphere formation, and enhance their sensitivity to temozolomide (TMZ). Subsequent study demonstrated that trim28 recruited histone deacetylase (HDAC) and DNA methyltransferase (DNMT) complexes to the CD133 promoter region, leading to localized chromatin compaction and gene silencing. This mechanism depends on the PhD bromo domain of TRIM28, signifying the specificity of its epigenetic regulatory function. Besides, there are also other mechanism that to do with TRIM28 and GBM. As for the therapeutic potential, TRIM28 can be used as a significant biomarker in GBM. Besides, CD133-targeted chimeric antigen receptor T cell may be a viable therapeutic approach to target CD133+ cancer stem cells in human glioblastoma or other treatment-resistant primary malignancies. Nonetheless, the precise mechanism of TRIM in GBM necessitates further investigation.

Keywords: GBM; TRIM; TRIM28; Tumor.

1. Background

Tumor is a common medical disorder defined by the abnormal proliferation of cells, leading to the formation of new tissue driven by various tumorigenic factors. It is seen in patients of diverse ages. The clinical manifestations of patients differ based on the lesion's location, the malignancy grade of tumor cells, and other factors.[1] As for gliomas, which are the most aggressive and commonly seen tumors in the adult CNS [2]. Besides they are also the most prevalent tumors that impact the CNS.

The 2007 World Health Organization (WHO) classification of primary CNS tumors categorizes gliomas into grade I tumors, including pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytomas; grade II tumors, such as oligodendrogliomas and astrocytomas; grade III tumors, comprising anaplastic oligodendrogliomas, anaplastic astrocytomas, anaplastic oligoastrocytomas, and anaplastic ependymomas; and grade IV tumors, specifically glioblastoma multiforme GBM.[3] Based on histological characteristics, the WHO classification of primary CNS tumors was significantly revised in 2016, categorizing gliomas into low-grade gliomas (LGGs) and high-grade gliomas (HGGs). The LGGs include grade I slowly proliferative gliomas and grade II infiltrative gliomas. The HGGs include grade III and grade IV anaplastic infiltrative gliomas, also known as GBM.[4]

As demonstrated by numerous studies, GBM exhibits one of the lowest 5-year overall survival (OS) rates of any human cancer and is one of the most fatal tumors. The median survival of GBM still approximately 16 months despite decades of relentless efforts by the research and medical communities to fight against this disease. Therefore, it is crucial to identify genes linked to novel therapeutic targets in order to enhance the effects on diagnosis, prognosis, and treatment in GBM.[5, 6]

2. TRIM

Tripartite motif (TRIM) is prevalent in multicellular organisms and displays variability across various species. Presently, more than 80 species have been identified inside the human body. The characteristic structural feature of TRIM is that the N-terminus of proteins has three conserved domains: the zinc finger domain, one or two B-box domains, and the CC (Coil) domain.[7, 8]

In recent years, research has found that TRIM can participate in various biological processes, both inhibiting tumor occurrence and promoting tumor proliferation and invasion. It can regulate the occurrence and development of tumors through multiple mechanisms.[9, 10]

3. The Possible Relationship between TRIM28 and GBM:

Recent studies indicates that CD133 plays a significant part between TRIM28 and GBM.

3.1. TRIM28:

It's obvious that, TRIM28 belongs to the TRIM protein family, which is a multifunctional transcriptional regulator involved in chromatin modification, DNA damage repair and stem cell stemness maintenance. Recent studies have found that trim28 affects the self-renewal and chemotherapy resistance of tumor stem cells by regulating the expression of

tumor stem cell markers such as CD133 in GBM.

3.2. CD133:

CD133, a glycoprotein with five transmembrane domains, is extensively used as a marker for isolating tumors, including liver cancer, glioma, and colon cancer. CD133 is expressed on both stem and differentiated cells. Growing data indicates that the N-glycan structure on the CD133 surface correlates with stem cell characteristics. During the development of tumor stem cells, the N-glycan structure on the surface of CD133 undergoes alterations. Hypoxia may augment the glycosylation of CD133 in glioma stem cells. Furthermore, modifying the glycosylation of CD133 might influence its stability or functionality. The N-glycosylation complex facilitates the secretion of CD133 by augmenting the interaction between CD133 and TSG101. Hypoxia-induced glycosyltransferase 8 domain 1 (glt8d1) enhances the maintenance of glioma stem cells by preventing the degradation of CD133. The correlation between the N-glycan structure of CD133 and stem cell characteristics remains ambiguous.[11]

Besides, other researchers have found that the interaction between CD133 and p85 activates the PI3K/AKT pathway, facilitating the self-renewal and tumorigenesis of glioma stem cells. Nonetheless, certain prevalent tumor cells also have CD133 expression. Prior research has indicated that the glycosylation of CD133 varies during the development of tumor stem cells. Besides Utilizing GBM stem cells as a model, it was observed that the diminished expression of glycosyltransferases, such as mannosidase man1a1, in tumor stem cells resulted in the development of a CD133 high mannose N-glycan structure. Following differentiation, the elevated expression of glycosyltransferases, including man1a1, transformed the CD133 N-glycan structure from a high mannose type to a complex type. In cancer stem cells, the high mannose type CD133 sustains the self-renewal capacity and tumor-initiating potential by facilitating the interaction between CD133 and the intracellular molecule DNMT1, thereby enhancing the expression of cell cycle inhibitors, preserving the low proliferation rate of glioma stem cells, and mitigating DNA damage.[12]

3.3. TRIM28 and CD133 and GBM:

3.3.1. Regulation of CD133 Expression

Research indicates that TRIM28 directly interacts with the promoter region of the CD133 gene via an epigenetic mechanism, suppresses histone acetylation (notably h3k27ac), and thus downregulates CD133 production. Knockdown of trim28 could markedly diminish the stem cell characteristics of GBM cells, impede tumor sphere development, and increase their susceptibility to TMZ.

3.3.2. Chromatin Reconfiguration and Epigenetic Repression

Subsequent research indicated that trim28 attracted HDAC and DNMT complexes to the CD133 promoter region, resulting in localized chromatin compaction and gene silence. This mechanism relies on the PhD bromo domain of trim28, indicating the specificity of its epigenetic regulatory activity.[13]

3.4. Suppression of Tumor Suppressor Genes

TRIM28 promotes tumor cell proliferation and survival by binding to and silencing the promoter regions of tumor suppressor genes such as PTEN and p53.

3.5. DNA Repair

TRIM28 is involved in non-homologous end joining (NHEJ) repair and may augment the resistance of glioblastoma (GBM) cells to radiation.[14]

3.6. a-Syn and tau

The detrimental gain-of-function of certain proteins in the brain is responsible for several neurodegenerative illnesses. Neurotoxicity in Parkinson's disease (PD) seems to be induced by increased levels of alpha-synuclein (a-Syn); Alzheimer's disease (AD) is marked by the buildup of tau in neurons; and both humans and model organisms undergo neurodegeneration due to heightened amounts of both proteins. Multiple lines of evidence suggest that tau and alpha-synuclein exhibit pathological overlap, notwithstanding the clinical differences between Alzheimer's disease and Parkinson's disease. We inquired if tau and a-Syn may be regulated by a same mechanism due to their associations. Consequently, we investigated genes that affect the post-translational levels of tau and alpha-synuclein. Our findings indicate that TRIM28 regulates tau and alpha-synuclein levels, and in animal models of tau- and alpha-synuclein-induced degeneration, its reduction mitigates toxicity.

TRIM28 enhances the stability and nuclear accumulation of both proteins, contributing to their toxicity. Intersecting screenings of comorbid proteinopathies show common processes and potential treatment targets.[14]

This may be the mechanism between TRIM28 and GBM either.

3.7. Nanobodies can Find the Existence of TRIM28 in GBM

The identification of heavy-chain-only antibodies (HCAbs) in camelids during the early 1990s appears to have opened a new window of opportunity in the field of targeted treatment approaches.[15] In the absence of light polypeptide chains, HCAbs form completely functional antigen-binding fragments consisting just of a single domain, referred to as the variable domain of the heavy chain of HCAbs (VHH) or nanobody. Nanobodies are small in size, stable even at elevated temperatures[16].These attributes make them appropriate for monitoring tumor biomarkers and developing enhanced diagnostic methodologies. The significant sequence similarity to human heavy chain variable domains (VHs) indicates reduced immunogenicity when used as treatments.[17]

Distinct nanobody:antigen pairings were identified, and mass spectrometry analysis indicated that two proteins, TRIM28 and bactin, were upregulated in GBM stem-like cells relative to the controls.[18]

3.8. miR-491

MicroRNAs are diminutive, non-coding RNAs that have a role in regulating several biological processes. MiRNAs identify their target sites by direct interaction with the 3' untranslated region (UTR) of the target mRNA. They may result in the destruction or translational suppression of the target mRNAs. Furthermore, each miRNA has the capacity to regulate more than one hundred mRNAs. It is believed that more than one-third of human genes are controlled by microRNAs. Numerous studies have clarified the involvement of miR-491 in carcinogenesis and tumor

development. Nakano et al. established that miR-491 was upregulated in colorectal cancer and facilitated apoptosis via the regulation of Bcl-XL. MiR-491 is associated with the metastasis of hepatocellular carcinoma via the suppression of Epithelial-Mesenchymal Transition (EMT) and the production of matrix metalloproteinases.[19-23]

Research has showed that the expression of miR-491 is inversely linked with the quantity of TRIM28 protein. Potential mRNA binding sites of miR-491, as predicted by TargetScan/MicroRNA, were validated by luciferase experiments. Clone creation and MTT tests demonstrated that the up-regulation of miR-491 suppressed the growth of glioma cells.[24]

4. Therapeutic Potential and Challenges

4.1. Inhibiting TRIM28

Inhibiting TRIM28 may enhance the effectiveness of current therapies via the following mechanisms:

Epigenetic agents: HDAC inhibitors (e.g., vorinostat) or DNMT inhibitors (e.g., decitabine) may counteract TRIM28-mediated gene suppression.

CRISPR-Cas9 gene editing of TRIM28 may markedly suppress the in vivo tumorigenic capacity of GBM cells.

4.2. TRIM28 can be Used as a Biomarker in the Diagnosis of GBM

The genes identified in the GBM biomarker panel were categorized into various signaling pathways based on biological pathways, including the AKT pathway (MYC, BMI1, EGFR, PIK3CA, PTK2, and UBC), the inflammation pathway (IRAK1 and APP), the P53 pathway (HDAC1, P53, and TRIM28), the WNT pathway (CTNNB1), and the mitochondrial signaling pathways (DAB1, PINK1, and RELN). AKT modulates angiogenesis and metabolic processes. Many human cancers have increased amounts of MYC, including glioblastoma multiforme (GBM). A link exists between Myc expression and glioma grade, and decreasing Myc in gliomas diminishes proliferation and enhances apoptosis.[25]

4.3. CD133

CD133 identifies self-renewing cancer stem cells (CSCs) in several solid tumors, and CD133+ tumor-initiating cells are recognized indicators of chemo- and radio-resistance in several aggressive malignancies, including glioblastoma (GBM), potentially contributing to intra-tumoral heterogeneity. We offer three immunotherapeutic approaches using a human anti-CD133 antibody fragment that targets a distinct epitope found in both glycosylated and non-glycosylated CD133, and we examine their impact on CD133+ cells in patient-derived models of GBM. We produced an immunoglobulin G (IgG) (RW03-IgG), a dual-antigen T cell engager (DATE), and a CD133-targeted chimeric antigen receptor T cell (CAR-T): CART133. All three exhibited effectiveness against patient-derived CD133+ GBM cells, with CART133 cells displaying enhanced efficacy in patient-derived GBM xenograft models, while not adversely affecting normal CD133+ hematopoietic stem cells in humanized CD34+ mice. CART133 cells may be a viable therapeutic approach to target CD133+ cancer stem cells in human glioblastoma or other treatment-resistant primary malignancies. [26]

5. Conclusion

As the most aggressive and fatal malignant glioma of the adult central nervous system, GBM has one of the lowest five-year overall survival rates, with a median survival of around 16 months, despite decades of sustained efforts by the scientific and medical communities to address this condition. Identifying genes linked to novel therapeutic targets in GBM is very important. TRIM is common in multicellular organisms and exhibits variations across different species. Recent study has shown that TRIM is involved in several biological processes, both suppressing tumor formation and facilitating tumor growth and invasion. TRIM28 is a member of the TRIM protein family, serving as a multifunctional transcriptional regulator implicated in chromatin remodeling, DNA damage repair, and the maintenance of stem cell pluripotency. Recent research indicates that trim28 influences the self-renewal and chemotherapy resistance of tumor stem cells via modulating the expression of tumor stem cell markers, including CD133, in GBM. TRIM28 also augments the stability and nucleus localization of a-Syn and tau proteins, hence enhancing their toxicity. Overlapping evaluations of comorbid proteinopathies reveal shared mechanisms and possible therapeutic targets. This may represent the mechanism between TRIM28 and GBM as well. Furthermore, research has shown that the expression of miR-491 is negatively correlated with the levels of TRIM28 protein. The potential mRNA binding sites of miR-491, predicted by TargetScan/MicroRNA, were confirmed by luciferase assays. The generation of clones and MTT assays indicated that the upregulation of miR-491 inhibited the proliferation of glioma cells.

TRIM28 may serve as a valuable biomarker for the diagnosis of GBM, highlighting its therapeutic potential. CART133 cells provide a potential therapeutic strategy for targeting CD133+ cancer stem cells in human glioblastoma and other treatment-resistant primary malignancies.

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