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Immune checkpoint expression and therapeutic implications in IDH1-mutant and wild-type glioblastomas

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Highlights

- Immune checkpoint inhibitors are promising anticancer therapeutics.
- Gliomas harbor *IDH1* mutation, whether they benefit from immunotherapy is unknown.
- *PDCD1* and *CD274* are commonly expressed in glioblastomas regardless of *IDH1* status.

- Glioblastomas may benefit from a standard immunotherapy.
- *IDH1*^{Mut} overexpress *PIK3R1* that requires a combination of PI3K/AKT/mTOR inhibitor.

Abstract

Programmed cell death protein 1 (*PDCD1*) and cluster of differentiation 274 (*CD274*) expression is implicated in escaping tumors from immune surveillance. Immune checkpoint inhibitors show promise in cancer therapy, yet their efficacy in glioblastomas, particularly with *IDH1* mutations, remains unclear. This study analyzed two independent NGS datasets (n = 577 and n = 153) from TCGA to investigate the expression of *PDCD1* and *CD274* in glioblastomas and their relationship with *IDH1* mutations. We used cBioPortal for mutation analysis, RNA seq for expression analysis, miRDB and miRabel for differential expression of miRNAs, and Kaplan-Meier for survival prediction. We found that 5.4% of glioblastomas harbored *IDH1* mutations, correlating with improved overall survival (OS) (p = 2.196e-3). Different glioblastoma cohorts showed a diverse *IDH1* mutational prevalence (4-31%). Despite this, *IDH1*^{Mu} was consistently associated with better OS (p = 8.235e-5). Notably, *PDCD1* and *CD274* were statistically significantly highly expressed in both *IDH1*^{Wt} ($p < 0.0001$) and *IDH1*^{Mu} tumors ($p < 0.0001$), with higher expression linked to poorer survival outcomes (*PDCD1:* p = 0.009; *CD274:* p = 0.02). Differential co-expression analyses revealed distinct gene and miRNA profiles for *IDH1*^{Wt} and *IDH1*^{Mu} glioblastomas, with specific upregulation of *PTEN* and downregulation of *MUC16* in *IDH1*^{Wt}, and upregulation of *PIK3R1* in *IDH1*^{Mu}. Additionally, *PIK3R1* and *ITGB2* emerged as critical druggable targets. Our findings indicate that *PDCD1* and *CD274* are highly expressed irrespective of *IDH1* mutation statuses, suggesting that glioblastomas could benefit from immunotherapy. Moreover, *IDH1*^{Mu} glioblastomas may require a combination of PI3K/AKT/mTOR inhibitors and immunotherapy due to *PIK3R1* overexpression.

Introduction

Isocitrate dehydrogenases (IDHs) catalyze several important reactions in various metabolic pathways including lipogenesis, Krebs cycle, and glutamine metabolism. The IDH has 3 isoforms such as IDH1, IDH2 and IDH3[1]. Particularly, the *IDH1* and *IDH2* genes are significantly mutated in various cancers including brain tumors2, 3, 4, 5. The *IDH1* mutations are highly prevalent in glioma cases, with >80% found in grade 2/3 cases[5,6]. Gliomas harboring *IDH1* mutations were found to have a better prognosis than *IDH1*^{Wt} cases[7,8]. The IDH1 and IDH2 proteins catalyze the reaction that converts isocitrate to α- ketoglutarate to make nicotinamide adenine dinucleotide phosphate (NADPH)[9]. NADPH has a strong reductive property that protects DNA from oxidative stress and the important path of NADPH production in the organs of the nervous system, is mostly driven by IDH1[10].

Glioblastomas (GBMs), the deadly and devastating brain tumors and are also classified based on

IDH1 statuses such as *IDH1*-wild type ($IDH1^{Wt}$) and *IDH1*-mutant ($IDH1^{Mu}$)[11]. Besides, the classification of diffuse gliomas is dependent primarily on the *IDH1* and *IDH2* mutation as per the 2021 update[12]. The $IDH1^{Wt}$ converts isocitrate to α-ketoglutarate, nevertheless, the $IDH1^{Mu}$ converts α-ketoglutarate to 2-hydroxyglutarate. Further, it has been shown that $IDH1^{Mu}$ is likely to lower the availability of this substrate which subsequently could reduce prolylhydroxylase domain (PHD) enzyme activity and result in the stabilization of HIF1α[8]. Analyses of expression, mutations, and epigenetic datasets revealed that $IDH1^{Wt}$ and $IDH1^{Mu}$ tumors might be different on a very fundamental level and could have different processes of tumorigenesis, however, the current differentiating factor between the two groups is their metabolic activity[13]. The present therapeutic options for GBMs involve surgery, and chemo-radiotherapy using temozolomide which still yields poor results with an estimated 5-year survival of 7.2%[14]. Current treatment poses various challenges such as the infiltrative GBM is nearly impossible to entirely resect the neoplasm along with the heterogeneity of cancer based on various epigenetic and genetic markers that would require tailored treatment options[6,15]. In human cancers including the malignancies arising from bladder, skin, lung, kidney, and blood, checkpoint inhibitor-mediated immunotherapy is becoming a promising therapeutic approach as it paves significant antitumor response with minimal side effects[16].

Immune-inhibitory checkpoint protein molecules including PD-1 (encoded by the gene, programmed cell death 1, *PDCD1*) and its ligand PD-L1 (encoded by the gene, cluster of differentiation 274, *CD274*) implicated remarkably in carcinogenesis and survival facilitating escape from tumor-neutralizing immune surveillance[16]. PD-1 is mainly expressed in immune cells including monocytes, T cells, B cells, dendritic cells, and tumor-infiltrating lymphocytes. The PD-L1 is expressed in tumor cells and antigen-presenting cells (APCs). Coupling of PD-L1 with PD-1 of T cells induce T cell-mediated functional suppression, exhaustion, neutralization, and interleukin-10 (IL-10) production in a tumor mass. This tumor expressing PD-L1 protects itself from T cell-mediated cytotoxic cell killing[17]. Many experimental studies have demonstrated that immune checkpoint inhibitors are promising therapeutics in gliomas[18,19]. Glioma cells express increased levels of intrinsic PD-L1 which limits the presentation of antigens, however, studies have found that inhibition of intrinsic PD-L1 reduces the tumor-infiltrating Treg cells and significantly increases long-term survival in mice[20]. Another study discovered combining stereotactic radiosurgery and anti-PD-1 immunotherapy increased median survival to 52 days compared to 27 days with radiosurgery alone in mice[21]. Besides, orthotopic GL261 tumors treated with anti-PD-1 alone reduced 44% of tumor size while combined with temozolomide tumor size reduction achieved 100%[18]. However, unlike aggressive malignancies such as metastatic melanomas and lung cancers, immunotherapy for the treatment of GBM has not shown great success due to the immunosuppressive microenvironment of GBM, tumor cells lacking tumor T cell infiltration leads to resistance to checkpoint inhibitors-mediated immunotherapy along with a lack of tumor antigens[22,23].

The anti-PD therapy has been successful in cancer; however, this was applied only to a particular type which is mostly due to heterogeneous or no expression of PD-1 in the niche of the malignancy. Current use of immunotherapy-mediated therapeutic options in glioblastoma has been limited while the present clinical trials are not finding promising results. Further,

expressions of intrinsic PD-1/PD-L1 and CTLA-4 from malignant tumor cells have been discovered to be potent mediators for neutralizing and escaping from immune editing[24]. However, whether glioblastomas bearing *IDH1*^{Wt} and *IDH1*^{Mu} could specifically benefit from the available immunotherapy is not completely known. Here, we explore the possibility of adopting immunotherapy in this aggressive glioma subtype by analyzing various gene/miRNA expressions *in silico* using two huge glioblastoma cohorts of TCGA and also identify potential drug targets by exploring unique expression patterns of genes.

Section snippets

Glioblastoma samples and datasets

We analyzed the next-generation sequencing (NGS) dataset of 577 glioblastoma samples from the TCGA (TCGA, Cell 2013)[25]. We used RNAseq data for expression of various genes analyzed including *PDCD1* (PD-1) and *CD274* (PD-L1). Mutational analysis was performed only for the *IDH1* gene in the glioblastoma dataset (n = 577). This large data set was preferred as it could increase generalizability, explore subgroups, and reduce sampling error. To corroborate that *IDH1* mutation plays a role in …

The *IDH1* mutations were detected in glioblastoma cases

We have analyzed the TCGA data set (TCGA, Cell 2013) consisting of 577 glioblastoma samples as described in the materials and methods[25]. We found 5.4% (31/577) of *IDH1* mutations in the glioblastoma cases. Of the 31 *IDH1*-mutated cases, 90.2% (28/31) of them harbored R132H while 6.5% (2/31) and 3.2% (1/31) had R132 G and R132C mutations, respectively (Fig. 1A & B).

To make a concrete conclusion that the *IDH1* mutation plays a role in glioblastoma tumorigenesis, we expanded our mutational analysis …

Discussion

Immune checkpoint inhibitor-mediated immunotherapy is a promising treatment in cancers including solid (kidney, lung, and melanoma) and hematopoietic malignancies (lymphomas and multiple myeloma)[34]. Yet, immunotherapy has not reached clinics for gliomas as treatment protocols are not well-standardized, and clinical trials lack clear information. Gliomas were shown to harbor highly frequent *IDH1* mutations and were classified based on the IDH1 mutant status[11,12]. However, whether glioblastomas …

Conclusion

In conclusion, *PDCD1* and *CD274* are highly expressed irrespective of *IDH1*^{Wt} and *IDH1*^{Mu} indicating that they have a prominent role in glioblastoma cell survival by aiding to escape from

immune surveillance suggesting a standard immunotherapy for glioblastomas. Analysis of *IDH1*^{Wt} and *IDH1*^{Mu}-specific unique gene expression revealed that *PIK3R1* is overexpressed only in *IDH1*^{Mu} cases suggesting that a combination therapy of PI3K/AKT/mTOR inhibitor either with an immunotherapy or a conventional …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AKM, SK, ASA …

Declarations

Ethics approval and consent to participate

The study was approved (RAC-2210035) by the Institutional Review Board (IRB) of King Faisal Specialist Hospital and Research Centre (KFSH & RC), Riyadh, Saudi Arabia.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article, all the datasets analyzed were from publicly available domains and were web linked appropriately in the article.

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