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Review on Bioinformatic Analysis of Druggable and Disease Causing Commonly Sharable Genes of Brain Cancer and Gliomas

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Abstract

Brain cancer, encompassing a range of tumors that either originate in the brain or metastasize from other body parts, presents a profound challenge in new drug discovery program due to its complexity and intricacies of its treatment. Identifying new drug target in brain cancer and gliomas is a challenging task considering the difficulties in drugs or molecules reaching into neuronal cellular compartments and blood brain barrier. Recent large-scale accumulation of bioinformatics information in gene-drug and gene-disease database resources yield promising approaches in identifying potential drug targets and understanding the molecular pathophysiology of brain neoplasms and gliomas. The Gene ontology databases and tools provide additional supporting evidence in identifying and validating newer drug targets through gene functional enrichments. This review highlights the importance of recently updated bioinformatics approaches in finding newer drug targets for diagnosis and therapeutics of brain neoplasms and gliomas.

Keywords: Brain Neoplasm; Glioma; Druggable Genes; Gene ontology and Drug targets

Abbreviations: WHO: World Health Organization; GBM: Glioblastoma Multiforme; TMZ: Temozolomide; TMs: Tumor Smaller Scale Tubes; MFA: Meclofenamate; PDOs: Patient-Derived Organoids; DMGs: Diffuse Midline Gliomas; QPOP: Quadratic Phenotypic Optimization Stage; BBB: Blood-Brain Obstruction; SPP1: Secreted Phosphoprotein 1; FUS: Focused Ultrasound

Introduction

Brain neoplasms and glioma affects millions globally and varies significantly in presentation, severity, and response to therapy. Primary brain cancers develop within the brain itself, while secondary brain cancers result from metastasis of tumors originating elsewhere in the body. Among primary brain cancers, gliomas are particularly notable due to their high prevalence and aggressive nature. Gliomas, which arise from the brain's supportive glial cells, account for a significant portion of primary brain tumors. These tumors are graded by the World Health Organization (WHO) from Grade I to IV, based on their aggressiveness. Grade IV gliomas, particularly Glioblastoma multiforme (GBM), represent the most severe and rapidly growing form of these tumors, often associated with a poor prognosis [1].

Recent advancements in glioma research have leveraged genetically engineered mouse models to identify specific subsets of tumor cells responsible for long-term tumor growth and resistance to treatment. These studies have highlighted the role of quiescent cells in sustaining tumor proliferation, even after temporary control with drugs like temozolomide (TMZ) [2]. Adult human GBM cells ought to be associated through an extensive syncytial communicating arrange by means of tumor smaller scale tubes (TMs), which are ultra-long membrane projections. It isn't clear how this arranges engineering relates to the transcribed cells within the body. Substances that meddled with this sort of network, for occurrence, meclofenamate (MFA), may well be valuable in glioblastoma treatment [3].

Diffuse midline gliomas (DMGs) develop diffusely and penetrate basic midline structures is one of the most traits of illness progression/proliferation in DMGs is related with dysregulation of the cell cycle by means of cyclins and cyclin subordinate kinases. Thinks about utilizing glioblastoma xenograft models illustrated the capacity of abemaciclib to cross the blood brain obstruction, increment survival, and diminish tumor development when given as a single operator or in combination with temozolomide [4].

High review astrocytic glioma (HGG) could be a deadly strong danger with tall repeat rates and restricted survival. Whereas a few cytotoxic operators have illustrated viability against HGG, sedate affectability testing stages to help in treatment determination are missing. Patient-derived organoids (PDOs) have been appeared to reliably protect the natural characteristics of a few cancer sorts counting HGG and coupled with the experimental-analytical half breed stage Quadratic Phenotypic Optimization Stage (QPOP) which assesses helpful affectability at a patient-specific level, may help as a device for personalized Therapeutic choices to progress treatment results for HGG patients. This proposition in this manner points to test the achievability of QPOP application in HGG, by to begin with setting up clinically significant HGG organoid models, taken after by the utility of QPOP-derived sedate combinations in HGG. We hypothesize that ideal QPOP-derived sedate combinations from clinically significant HGG organoids can coordinate administration and move forward results of HGG patients. In expansion, given the nature of the blood-brain obstruction (BBB) which postures noteworthy challenges to systemic treatment of brain tumors, this presents of an opportunity to look at the relationship between individualized tumors evaluated by novel radiopharmaceutical-based neuroimaging and clinical results [5].

Bioinformatics and Gene Ontology resources

As per literatures, gene ontology databases, drug databases and drug-gene database resources, several hundreds of ligands, new molecules and approved drugs are in pipeline. Recent enormous data accumulation of drug-disease and drug–gene interaction databases resulted in huge wealth of details about molecular functions, cellular compartments and biological process of genes in normal and diseased state [6-8].

Recent developments in genomic medicine yielded newer approaches in diagnosis and therapeutics in brain cancer and gliomas. (Figure 1) depicts flow chart for strategies and steps involved in finding potential gene targets in diagnosis and therapeutics of brain cancer and gliomas. Accurate classification of cancers using genetic biomarker will be promising in cancer therapeutics. Identifying such potential biomarkers and drug targetable proteins through bioinformatics approaches involves collection of relevant curated disease genes and classifying commonalities between brain neoplasms and gliomas (Figure 2). Functional enrichment analysis of crucial genes using gene ontology resources/tools provides comprehensive bioinformatics model in molecular pathophysiology. Browsing through such tools help users to search, visualize and download user friendly and interpretable curated data by specifying with suitable search parameters.

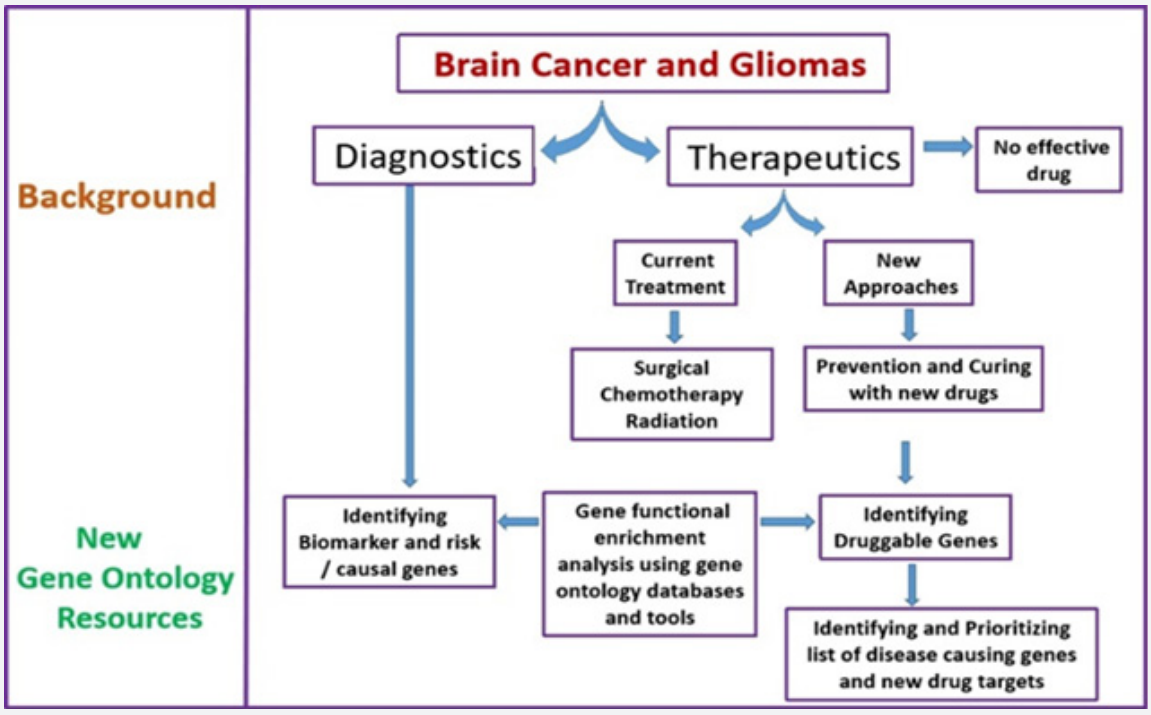

Figure 1: Graphical representation of bioinformatic approaches in finding new disease causing genes and new drug targets in Brain cancer and Gliomas.

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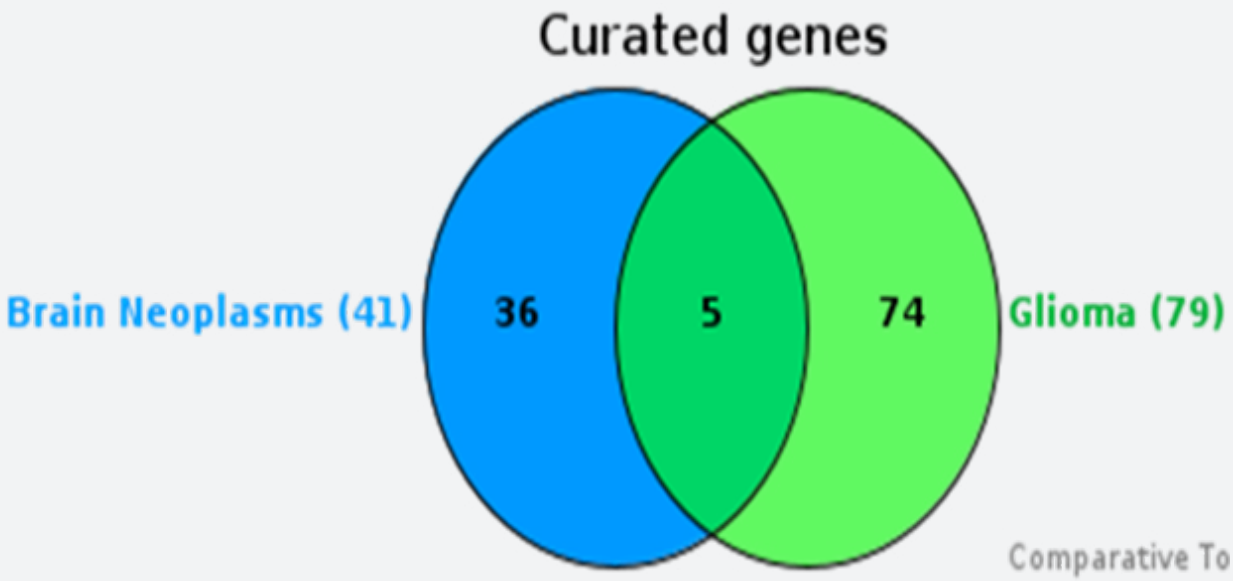

Figure 2: Number of genes reportedly associated with brain neoplasms, gliomas and genes which are commonly shared between them. (Comparative toxicogenomic database, https://ctdbase.org/).

In clinical practice, brain cancer and gliomas are diagnosed using neuroimaging techniques and biopsy samples. Blood derived promising genetic biomarkers enable easy diagnostic, molecular profiling, targeted therapy and monitoring response to treatment. Comparative toxicogenomic database (https://ctdbase.org/) is commonly used in finding curated information about chemical-gene/protein interactions and gene-disease relationships. According to this database, a total of 115 genes reported in brain neoplasms and glioma, out of which five genes namely CDKN2A, HRAS, MGMT, SPP1 and TRP53 were commonly shared between brain neoplasms and gliomas. The clinical relevance of these gene expressions in such cancers need to be explored for validating them as biomarkers by understanding network of their functional relationships using gene ontology resources. The molecular functions of these sharable genes were found involved in enzyme activities, protein binding in signal transduction, methyltransferase, cellular defense, cell proliferation and tumor suppressor activities (Table 1).

Table 1: The molecular functions of the commonly shared genes of brain neoplasm and gliomas. The gene drug ability data with number of available active ligands and approved drugs as reported in three different open source databases.

S. No	Gene	Molecular Function	Gene Druggability					
			Pharos database		Bindingdb database		Dgidb database	
			Interactive ligands	Drug approved	Interactive ligands	Drug approved	Interactive ligands	Drug approved
1	CDK-N2A	Cyclin-dependent kinase inhibitor 2A; Acts as a negative regulator of the proliferation of normal cells by interacting strongly with CDK4 and CDK6.	Nill	Nill	Nill	Nill	26	15
2	HRAS	GTPase HRas, N-terminally processed; Involved in the activation of Ras protein signal transduction. Ras proteins bind GDP/GTP and possess intrinsic GTPase activity.	19	2	62	Nill	76	31
3	MGMT	Methylated-DNA-protein-cysteine methyltransferase; Involved in the cellular defense against the biological effects of O6-methylguanine (O6-MeG) and O4-methylthymine (O4-MeT) in DNA.	35	Nill	Nill	Nill	33	15

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4	SPP1	Osteopontin; Binds tightly to hydroxyapatite. Appears to form an integral part of the mineralized matrix. Probably important to cell-matrix interaction.	Nill	Nill	Nill	Nill	15	7
5	TP53	Cellular tumor antigen p53; Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type.	14	Nill	Nill	Nill	453	301

All these genes were found druggable, since several interactive ligands were reported, and a few drugs have already received regulatory approval for human clinical trials. Out of these five genes, TP53 and HRAS were found to interact with highest number ligands with more, number of regulatory approval for human clinical trials. The important molecular functions of all five genes with functional enrichments up to 200-fold was depicted in (Figure 3). Other than gliomas, these genes functional roles were also described in bladder cancer, melanoma, lung cancer, pancreatic cancer and leukemia. Wherein, P53 signaling, toll like receptor signaling and apelin signaling pathways were found to influence in molecular functions. Hierarchical clustering of functions with signaling pathways indicated varied levels of correlation significances of these five genes (Figure 4).

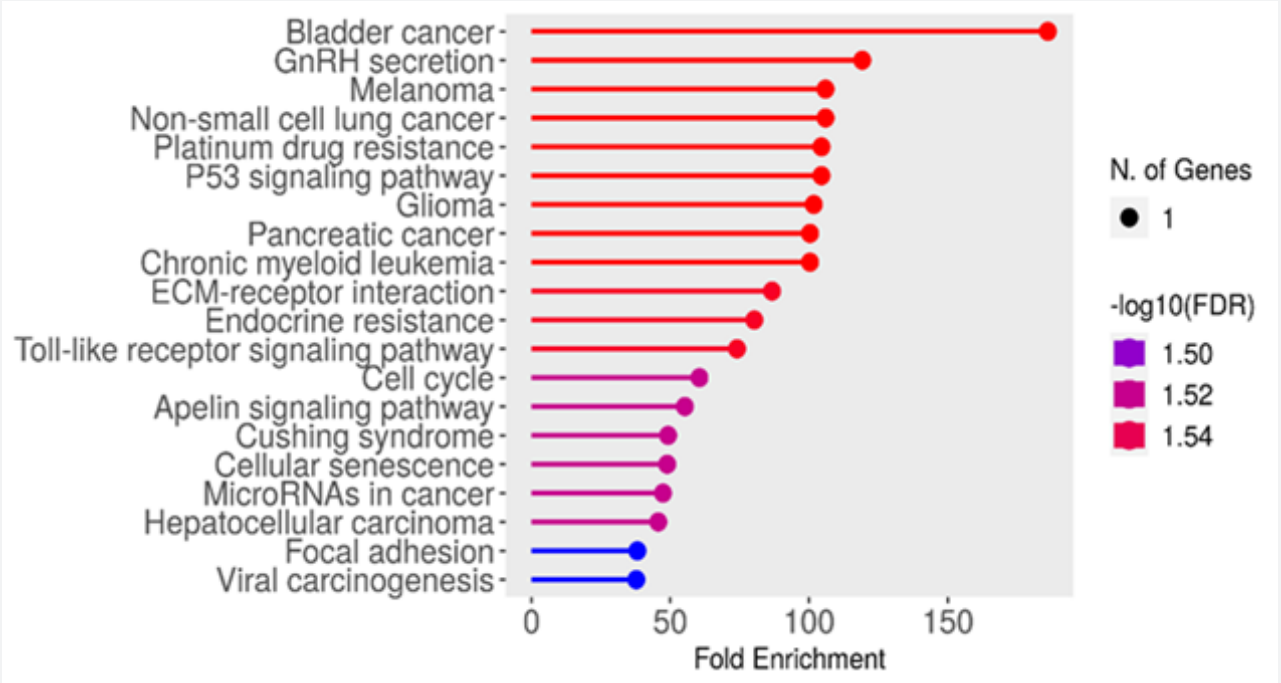

Figure 3: Shiny GO Bar plot showing functional enrichments of commonly shared brain neoplasm and gloma genes. The number of folds in functional enrichments with FDR (false discovery rate) values are graphically represented.

Functional Relationship Between Commonly Sharable Genes in Brain Cancer

The functional association of TP53 and CDKN2A in head and neck cancer was earlier described as predictive biomarkers [9,10]. The increased CDKNA2A expression n aggressive meningiomas and gliomas was earlier described in brain cancer and gliomas [11,12]. The functional diversity of GTPase (HRAS) was earlier described in neurofibromatosis type 1 cancer predisposition [13,14]. The overexpression of MGMT and its negative regulation of DNA repair mechanisms in glioblastoma were evaluated for potential therapeutic benefit using glioblastoma cell line [15]. The intercellular communication of Osteopontin (SPP1) was earlier described as a biomarker in tissue damage in response to brain injury and cancers [16,17].

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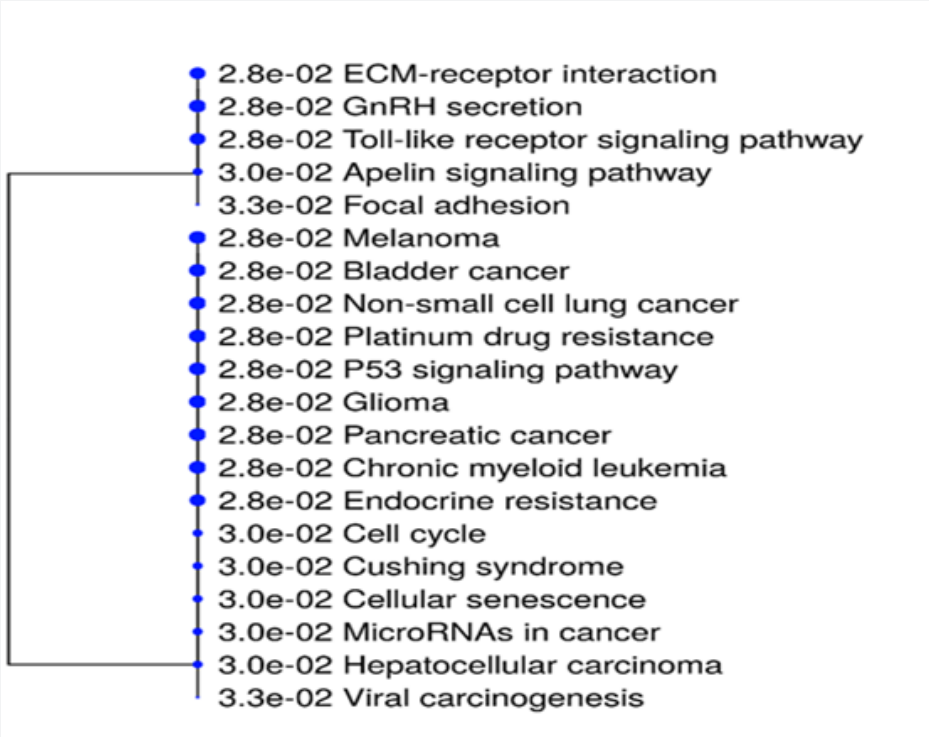

Figure 4: ShinyGO database hierarchical clustering of tree correlation among significant pathways enriched with tested 5 genes. Pathways having commonly shared genes are clustered together. Bigger dots indicate more significant P-values.

In central nervous system cancer, the TP53 gene expression was considered in profiling methylation activity, which was demonstrated as promising diagnostic biomarker in nervous system tumors [18,19]. GBM, a particularly aggressive type of glioma, can occur spontaneously as primary GBM or develop from lower-grade astrocytomas as secondary GBM. The genetic landscape of GBM is marked by various abnormalities, including EGFR amplification, p16/INK4a deletion, and PTEN mutations, which vary between primary and secondary forms [20]. These genetic variations contribute to the complexity of diagnosis and the need for personalized treatment approaches. particularly focusing on critical genes such as CDKN2A, HRAS, MGMT, SPP1, and TP53, which play pivotal roles in tumor biology and therapeutic responses. CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A) is a crucial tumor suppressor gene known for its role in regulating the cell cycle and maintaining genomic stability. It encodes two key proteins, p16INK4A and p14ARF, which are essential in preventing uncontrolled cell proliferation.

In brain neoplasms, particularly gliomas and glioblastomas, mutations or deletions in CDKN2A significantly affect tumor progression and patient prognosis, making it a critical focus for understanding tumor biology and developing targeted therapies. HRAS, a member of the Ras family of oncogenes, plays a vital role in cellular signaling pathways that govern growth, differentiation, and survival. As a small GTPase, HRAS is involved in key pathways that impact tumor development and progression. Its dysregulation in brain neoplasms highlights its significance in understanding tumor behavior and identifying potential therapeutic targets. MGMT(O6-Methylguanine-DNA Methyltransferase) is a crucial DNA repair enzyme that maintains genomic stability by repairing DNA damage caused by various mutagens. Its role in removing alkyl groups from DNA is particularly relevant in brain neoplasms, where MGMT's function and expression levels influence tumor behavior, treatment response, and overall patient outcomes, especially in gliomas and glioblastomas [21].

SPP1 (Secreted Phosphoprotein 1), also known as osteopontin, is a multifunctional extracellular matrix protein involved in processes such as cell adhesion, migration, and immune responses. In cancer biology, SPP1's role in tumor growth, progression, and metastasis is of significant interest. Its involvement in brain neoplasms underscores the importance of extracellular matrix components in tumor development and progression. TP53, often referred to as the "guardian of the genome," is a pivotal tumor suppressor gene that encodes the p53 protein. This protein is essential for maintaining genomic stability by regulating the cell cycle, facilitating DNA repair, and inducing apoptosis in response to cellular stress or DNA damage. TP53 mutations are prevalent in various cancers, including brain neoplasms, where they critically

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influence tumor development, progression, and therapeutic responses [22].

The use of ganciclovir to ablate these cells has shown promise in arresting tumor growth, offering potential pathways for novel therapeutic interventions. One of the significant challenges in treating brain tumors is the blood-brain barrier (BBB), which impedes the effective delivery of systemic therapies. Innovations such as focused ultrasound (FUS) have emerged as promising techniques to temporarily open the BBB, thereby enhancing drug delivery and potentially improving treatment outcomes. Clinical trials have demonstrated the feasibility of FUS in controlling BBB permeability, presenting new opportunities for targeted therapeutic approaches [23]. Genes such as CDKN2A, HRAS, and TP53 play crucial roles in regulating the cell cycle. Disruptions in these pathways can lead to uncontrolled cell proliferation and contribute to tumor progression. MGMT is essential for DNA repair mechanisms. Its dysfunction can lead to genomic instability and is critical in the development of glioblastoma. HRAS is involved in cell signaling pathways that affect growth and differentiation. Abnormalities in these pathways can promote tumor development. SPP1 is important for cell adhesion, influencing tumor growth and metastasis. Disruptions in cell adhesion mechanisms can enhance tumor invasiveness. Epigenetic changes, such as EGFR amplification and p16/INK4a deletion, significantly affect tumor growth and development by altering gene expression without changing the DNA sequence.

Recent research has identified a subset of endogenous tumor cells that sustain long-term glioma growth, presenting potential targets for new therapeutic strategies. The BBB remains a major obstacle for effective brain tumor treatment. Techniques like FUS are being explored to improve drug delivery across this barrier. Understanding these pathways is crucial for advancing the diagnosis and treatment of brain neoplasms. This review will highlight the current state of research, focusing on the interplay between genetic factors, key biological pathways, and innovative therapeutic approaches. By analyzing insights from genetic studies, experimental models, and emerging treatment strategies, this review aims to provide a comprehensive overview of the latest advancements in brain neoplasms research and their implications for future clinical practice.

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