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Bioinformatics screening of gene expression profile and diagnostic application of meningeal carcinoma

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Abstract. – OBJECTIVE: The aim of this study was to research gene expression profiles and diagnostic applications of meningeal carcinoma based on bioinformatics.

MATERIALS AND METHODS: We used the Gene Expression Omnibus (GEO) database to obtain the GSE43290 dataset based on the expression data of normal meninges and meningiomas consisting of 51 samples divided into two groups (47 samples of meningioma tumors and four samples of normal meninges). We used the GEO2R tool to identify differentially expressed genes (DEGs) by setting the log2 fold change as greater than two and an adjusted p-value lower than 0.05. We used the database for annotation, visualization and integrated discovery (DAVID) to perform gene ontology, biological pathways and functional annotation of the DEGs. A search Tool for the Retrieval of Interacting Gene database (STRING) was used to obtain Protein-Protein Interaction (PPI) and modular networks based on the Markov clustering algorithm.

RESULTS: Our study identified 358 significant DEGs, of which 343 were downregulated genes while 15 were upregulated. Five significant hub genes (*CXCL8*, *AGT*, *CXCR4*, *CXCL12* and *CXCL2*) were associated with various biological pathways, molecular functions and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The DEGs were enriched in biological pathways of chemokine-mediated signaling, positive regulation of leukocyte chemotaxis, second messenger-mediated signaling, induction of positive chemotaxis, CXCR chemokine receptor binding and activities of cytokines.

CONCLUSIONS: These hub genes and pathways could be targeted in clinical research to discover new treatments for meningeal carcinoma.

Key Words:
Meningioma carcinoma, Hub genes, Bioinformatics, Biological pathways, Molecular functions.

Introduction

Meningeal carcinomas are benign tumors that can be treated with surgical operations[1], with about 25% of patients experiencing relapse. Recurrent meningiomas are predicted based on histopathological examinations and the tumor grade. For instance, grade I meningiomas are associated with recurrence or relapse. These tumors are primarily benign, with no clear relationship between various types of tumors and patient outcomes.

Meningeal carcinomatosis is a medical condition that involves cancer cells that grow from the primary sites to the meninges. Meninges are the thinner tissue layers that offer cover and protection to the spinal cord[2,3]. Meningeal carcinomatosis causes meninges inflammation, cerebrospinal fluid build-up, and pressure in the cerebellum. Aarhus et al[4] reported that meningiomas are among the largest intracranial neoplasms in about 40% of cases worldwide. Mutations of the neurofibromatosis type 2 (*NF2*) gene on the chromosome 22q12.2 have increased the pathogenesis of meningiomas. The loss of the *NF2* gene leads to an autosomal syndrome that enhances the growth and development of several meningiomas.

Aarhus et al[4] suggested that sporadic meningiomas have the greatest loss of heterozygosity in 70% of recorded cases and mutations in 60%. The mechanisms of meningioma are based on the Knudsons dual hit hypothesis. Initially, the risk allele undergoes deletion followed by mutations in the other allele containing tumors-suppressing genes associated with neoplastic growth. However, this mechanism is not exclusively responsible for the growth and development of meningiomas, and other molecular and biological pathways are associated with the growth and development of meningiomas[5,6].

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Additionally, the role of other cell types and signalling pathways in meningioma development is being actively investigated. For example, the interaction between tumor cells and the microenvironment, including immune cells, stromal cells, and blood vessels, may play a crucial role in the pathogenesis of this disease.

Magnetic resonance imaging (MRI) is the primary technique to distinguish between atypical and benign meningioma[7,8]. Pathological diagnosis of meningioma can reveal malignant proliferation or metastasis in benign tumors. Meningiomas are primarily found in the brain and spinal cord; however, some meningiomas could develop in the venous sinuses. Surgical resections are the most essential treatment for meningiomas with a lower degree of recurrence[9-11]. Cytogenesis of meningiomas is associated with monosomy of the 22 or 22q and mutations of *NF2* genes; however, they have a limited prognostic significance[12,13]. The exact cytogenesis of meningioma cells is unclear and not explicitly understood; however, recent studies[12,13] have suggested that it begins in the arachnoid cap cells situated in the arachnoid membrane in the brain and spinal cord.

Meningioma cells are derived from the neural crest and can form tumors due to their ability to proliferate and differentiate[14,15]. The accumulation of genetic mutations and chromosomal abnormalities may transform these cells into meningioma cells. Recent studies[16-18] have suggested that meningiomas may also arise from a subset of stem cells in the arachnoid membrane, known as meningothelial stem cells. These cells have the potential to differentiate into various cell types and may give rise to meningioma cells under certain conditions. Chromosomal mutations and abnormalities in the complex karyotypes have been associated with poor outcomes in meningioma.

Bioinformatics has allowed researchers to identify gene expression profiles and significant hub genes associated with the growth and development of meningiomas. Furthermore, identifying differentially expressed genes (DEGs) allows the discovery of significant biomarkers associated with the growth and progression of meningiomas[19]. Our study will also analyze the potential links between hub genes and how they enhance the development of meningiomas.

Bioinformatics reduces the limitations of conventional biology on molecular mechanisms, which describes a partial viewpoint of the individual variations and functions of particular genes, mRNA or proteins. The main objective of our study is to analyze the gene expression profile and diagnostic application of meningeal carcinoma based on bioinformatics.

Materials and Methods

Microarray Datasets

Our study used the gene expression omnibus (GEO) database from the National Center of Biotechnology Information (https://www.ncbi.nlm.nih.gov/geo/) to obtain microarray datasets associated with meningioma. We used the keywords "meningioma" and "meninges" to obtain the following datasets. The GSE43290 dataset is based on the expression data of normal meninges and meningiomas. The dataset correlated the gene expression profiles with the relevant cytogenetic groups of meningiomas. The dataset was based on the GPL96 platform (Affymetrix Human Genome U133A Array), consisting of 51 samples divided into two groups (47 meningioma tumors and four normal meninges). We converted all probes into their corresponding gene symbols.

Differentially Expressed Genes (DEGs)

Our study adopted the GEO2R tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE43290) to identify DEGs. Our analysis used the predefined experimental groups of meningioma tumors and normal meninges. Furthermore, we removed genes that did not have symbols and those genes that consisted of more than one probe. We set the $\log_2$ fold change as greater than two and used an adjusted p-value lower than 0.05 to identify statistically significant genes. The same tool was used to obtain Venn diagrams for analyzing overlapping DEGs and produced the corresponding volcano and mean difference plots. We used the Express Network Analyst (https://www.networkanalyst.ca/) to analyze the gene matrix files and produce the heatmap of DEGs.

Gene Ontology (GO) and KEGG Pathways

We used the database for annotation, visualization, and integrated discovery (DAVID) (https://david.ncifcrf.gov/) to perform gene ontology, biological pathways, and functional annotation of the DEGs. The Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.genome.jp/kegg/pathway.html) database revealed pathways

of molecular interactions in meningiomas. We set the gene counts to greater than or equal to 10, with a false discovery rate (FDR) based on an adjusted *p*-value lower than 0.05 as statistically significant. GO analyses revealed the DEGs' molecular functions, biological processes and cellular components.

Protein-Protein Interaction (PPI) Networks and Modular Analysis

We used the Search Tool for the Retrieval of Interacting Gene database (STRING) to examine the interactions between various proteins (https://string-db.org/). Based on the Markov clustering algorithm, we exported the DEGs into the STRING tool to obtain significant interactions among various networks. The interaction score was set to greater than 0.9. after which the PPI networks were exported to Cytoscape for further analysis. In Cytoscape, we used the Molecular Complex Detection to examine densely connected regions based on the topological networks. Statistically significant networks were detected based on a cut-off degree of 0.2, a maximum depth of 100 and a k-core of 2.

In Cytoscape (https://cytoscape.org/), we used the CytoHubba to rank various nodes in the PPI networks. We identified the top 10 genes based on degree, centrality, and neighborhood components. Overlapping genes were considered statistically significant hub genes.

Statistical Analysis

We performed statistical analysis using GEO2R tool to screen and identify differentially expressed genes. In all analyses, statistical significance was inferred at a $p < .05$ and the $\log_2$ fold change was greater than 1.

Results

We used the GSE43290 dataset from the GEO database. The dataset had 51 samples grouped into meningioma tumors (N = 47) and normal meninges (N = 4). We processed the data through a $\log_2$ transformation while accounting for batch effects on all gene expression profiles. Our analysis involved tools such as GEO2R and Network Analyst that generated the differentially expressed genes. Our study identified 358 significant DEGs, of which 343 were downregulated genes while 15 were upregulated. These DEGs were screened based on the selected criteria of a log fold change of greater or equal to 2 and an adjusted *p*-value lower than 0.05.

The normalized boxplots (Figure 1) reveal a successful $\log_2$ transformation to normalize the gene expression profiles. The median values confirmed effective transformation and normalization, which allows multiple cross-comparisons in all groups.

Volcano Plot

According to Figure 2, we generated the differentially expressed genes in GEO2R based on an adjusted *p*-value lower than 0.05 and a $\log_2$-fold change. Log_2-fold change represents the magnitude of change and defines the proportion of transcript-expressed values to the logarithm of the genes. The volcano plot represents annotated genes; the blue section represents downregulated genes. Downregulated genes are those whose expression levels were limited in meningioma tumors compared to normal meninges. The red section represents upregulated genes. Upregulated genes are those whose expression levels were increased in meningioma tumors compared to normal meninges. The black section represents genes with no statistical significance.

Mean Difference Plot

According to Figure 3, the mean difference plot represents the differences (intensity ratios of logs) against the means (average log intensities). Every point on the mean difference plot is a point of gene annotation. The blue section represents downregulated genes. Downregulated genes are those whose expression levels were limited in meningioma tumors compared to normal meninges. The red section represents upregulated genes. Upregulated genes are those whose expression levels were increased in meningioma tumors compared to normal meninges. The black section represents genes of no statistical significance. Genes of higher expression levels are situated on the far left, while genes of lower expression levels are situated on the far right. We observed that genes of lower expression values had the greatest fold change and vice versa. Therefore, there is a fanning effect as the differentially expressed genes tend to move from the right to the left.

Heatmap

PPI networks and modular analysis

Our PPI networks and modular analysis produced 324 edges and 341 nodes (Figure 4). In Fig-

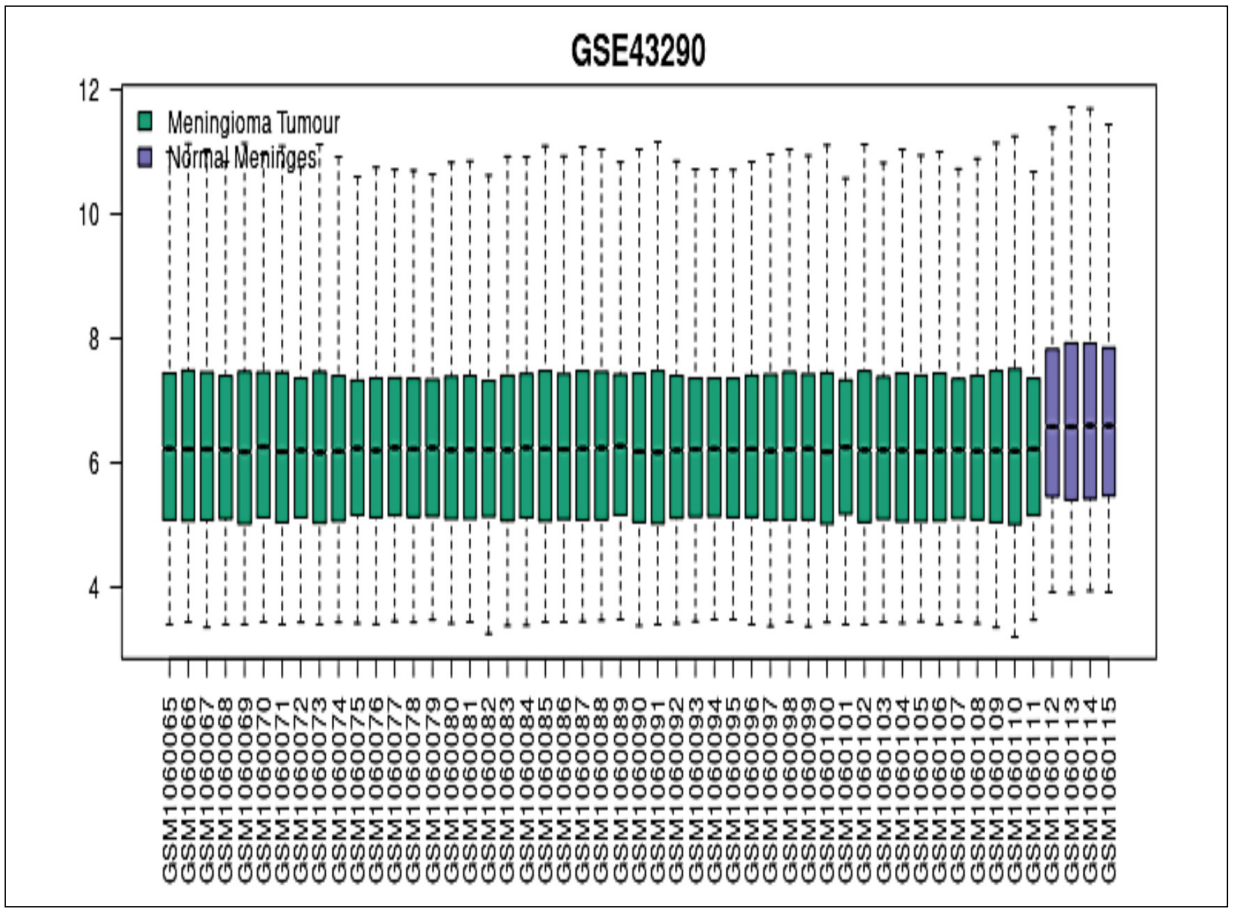

Figure 1. Boxplots of normalized gene expression profiles. The x-axis shows the genes, while the y-axis represents their expression profiles.

ure 4, the red marks indicate upregulated DEGs, while the green regions represent downregulated DEGs. Modular analysis (Figure 4) showed a network of 14 nodes and 91 edges.

According to Figures 4 and 5, there were five significant hub genes. *CXCL8* (C-X-C motif chemokine ligand 8) is a gene that encodes interleukin-8 (*IL-8*). *IL-8* is a member of the *CXC* chemokine family and is involved in regulating immune responses, inflammation, and angiogenesis. The *AGT* (angiotensinogen) gene encodes a precursor protein called angiotensinogen, a key component of the renin-angiotensin system (RAS) that regulates blood pressure and fluid balance in the body. *CXCR4* (C-X-C chemokine receptor type 4) is a gene that encodes a receptor protein called *CXCR4*, a member of the G protein-coupled receptor superfamily. The *CXCL12* (C-X-C motif chemokine ligand 12) gene encodes a protein called *CXCL12*, also known as stromal cell-derived factor-1 (*SDF-1*). *CXCL12* is a member of the chemokine family of proteins involved in various cellular processes. Lastly, the *CXCL2* gene encodes a macrophage inflammatory protein-2 alpha (*MIP-2 alpha*) protein. *CXCL2* is a member of the chemokine family of proteins and is produced by various cell types, including macrophages, neutrophils, and epithelial cells.

KEGG and GO Pathways of Hub Genes

According to Figure 6, the hub genes were enriched in KEGG pathways of chemokine signaling, cytokine-cytokine receptor interactions, *NF-κB* signaling pathway, pathways in cancer, human cytomegalovirus infection, the intestinal immune network for IgA production, legionellosis, salmonella infection, rheumatoid arthritis, *IL-1*7 signaling pathway and leukocyte transendothelial migration. The chemokine signaling pathway is involved in producing chemokines, expression of receptors and numerous cellular responses.

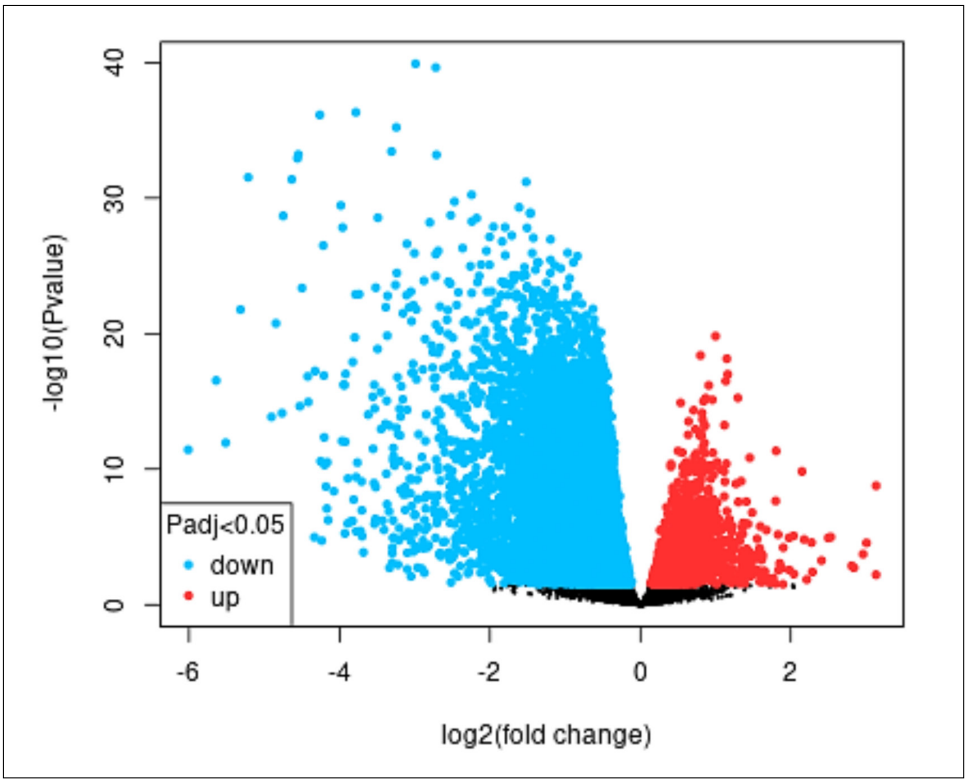

Figure 2. Volcano plot.

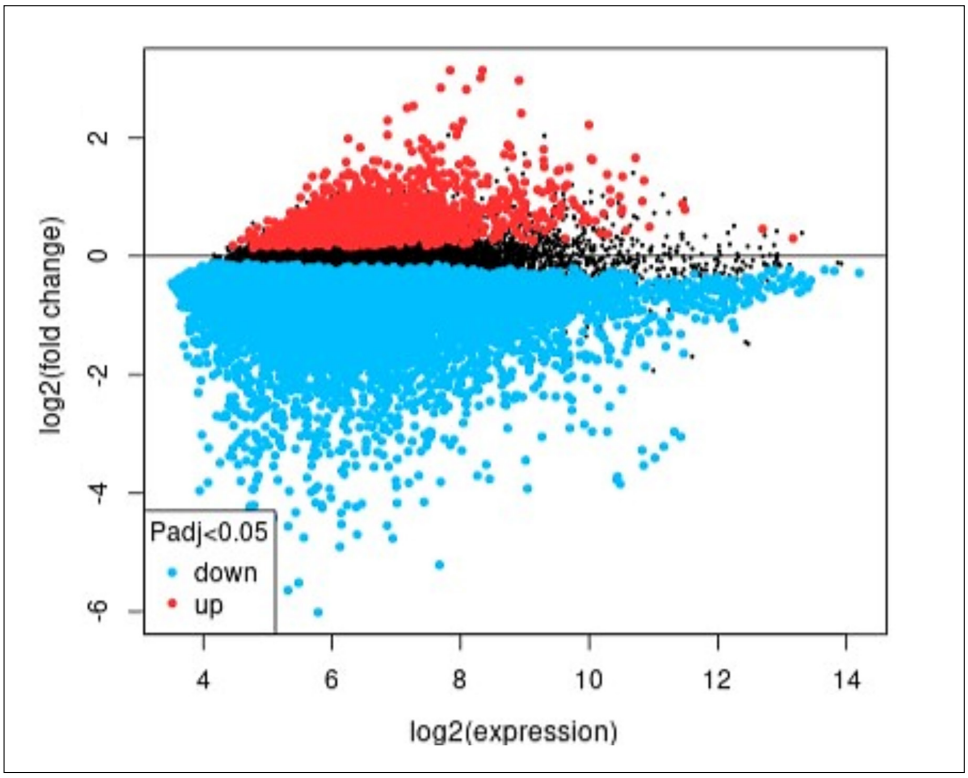

Figure 3. Mean difference Plot.

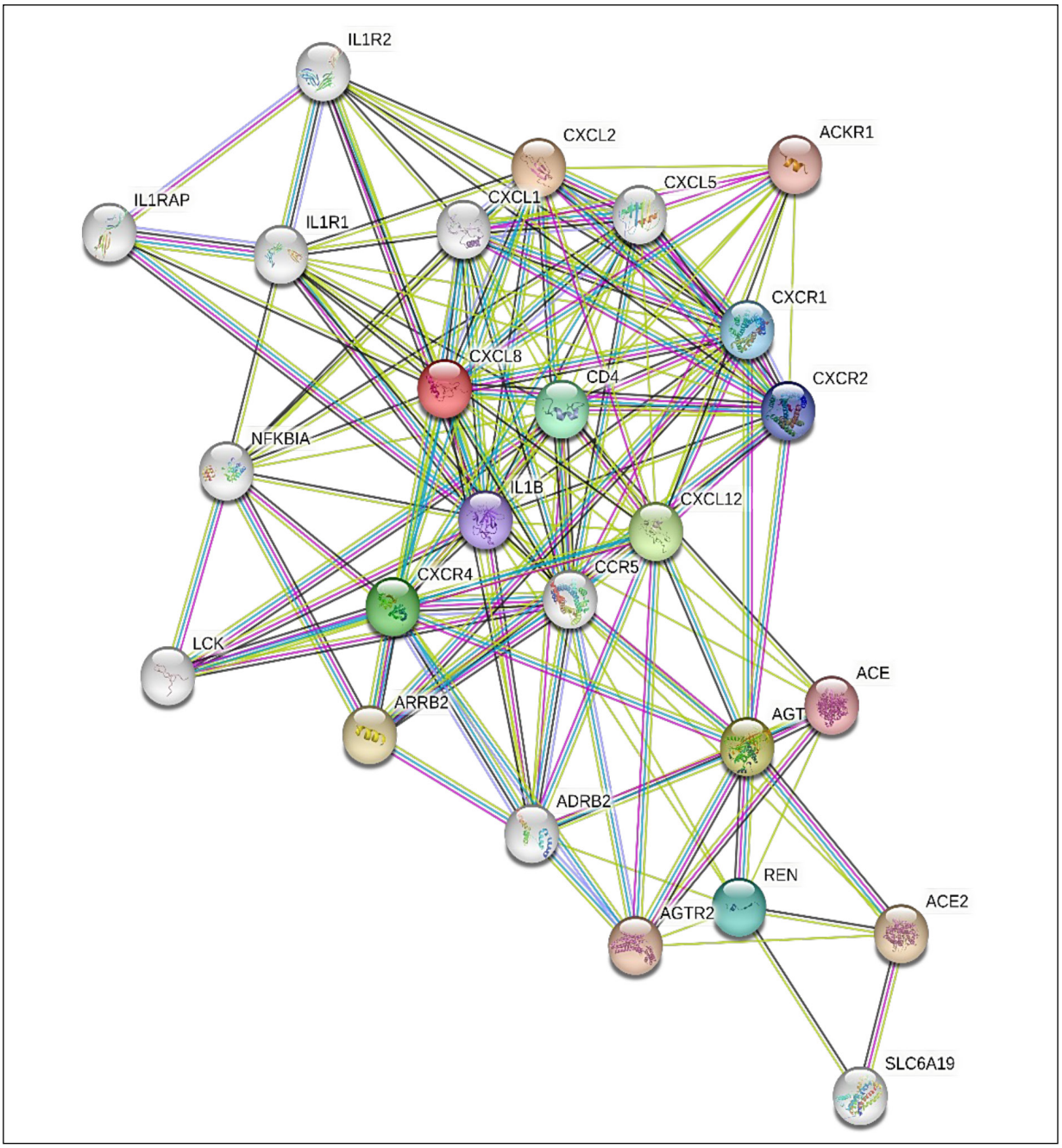

Figure 4. PPI Networks of DEGs.

Cytokine-cytokine receptor interactions pathway regulated the immune system and signaling of various cell molecules. The leukocyte transendothelial migration (LTEM) pathway is a complicated pathway involving the migration of leukocytes across the endothelial barrier into the tissues and cells in response to pathogens. The nuclear factor kappa B (*NF-κB*) pathway is essential in controlling various biological processes, such as the survival of cells' inflammatory and immune responses. All these pathways were significant in the growth and development of meningioma.

Chemokine signaling is involved in meningioma by regulating leukocyte recruitment and activation within the tumor microenvironment. Chemokines are a family of small signaling proteins that regulate the migration and activation

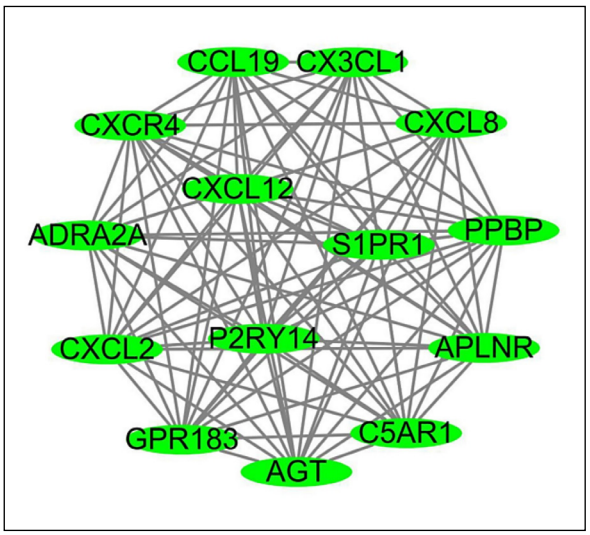

Figure 5. Modular Analysis. The green color represents downregulated genes.

of leukocytes in response to inflammation, tissue damage, and infection. NF-kappa B is a transcription factor that regulates gene expression in various cellular processes, including cell proliferation, differentiation, and survival. The pathway regulates biological processes, including inflammation, immune response, and cell survival.

Cytokine-cytokine receptor interaction pathway involves cytokines that play important roles in cell signaling and immune system regulation. They bind to specific cytokine receptors on the surface of target cells, triggering a series of downstream signaling events that can ultimately affect cell behavior, such as proliferation, differentiation, and survival.

Biological, Cellular and Molecular Enrichment Pathways

According to Table I, in the Biological Process (BP) category, there are various GO terms with associated gene counts, ranging from 10 to 32, and corresponding False Discovery Rates (FDR). Similarly, in the Cellular Component (CC) category, there are terms with gene counts ranging from 13 to 81 and FDR values. Lastly, the Molecular Function (MF) category has the term "integrin binding" with a gene count of 11 and an FDR value.

Discussion

Our study identified five critical hub genes in the growth and development of meningioma. These hub genes included *CXCL8*, *AGT*, *CXCR4*, *CXCL12* and *CXCL2*. They were enriched in biological pathways of chemokine-mediated signalling, positive regulation of leukocyte chemotaxis, second messenger-mediated signalling, induction of positive chemotaxis, *CXCR* chemokine receptor binding and activities of cytokines.

KEGG_PATHWAY	Chemokine signaling pathway	1.21E-05	CXCL8;CXCL12;CXCR4;CXCL2
KEGG_PATHWAY	Cytokine-cytokine receptor interaction	3.48E-05	CXCL8;CXCL12;CXCR4;CXCL2
KEGG_PATHWAY	NF-kappa B signaling pathway	1.06E-04	CXCL8;CXCL12;CXCL2
KEGG_PATHWAY	Pathways in cancer	1.84E-04	CXCL8;CXCL12;CXCR4;AGT
KEGG_PATHWAY	Human cytomegalovirus infection	8.51E-04	CXCL8;CXCL12;CXCR4
KEGG_PATHWAY	Intestinal immune network for IgA production	0.002881915	CXCL12;CXCR4
KEGG_PATHWAY	Legionellosis	0.003249738	CXCL8;CXCL2
KEGG_PATHWAY	Salmonella infection	0.006977051	CXCL8;CXCL2
KEGG_PATHWAY	Rheumatoid arthritis	0.006944943	CXCL8;CXCL12
KEGG_PATHWAY	IL-17 signaling pathway	0.006528466	CXCL8;CXCL2
KEGG_PATHWAY	AGE-RAGE signaling pathway in diabetic complications	0.006862441	CXCL8;AGT
KEGG_PATHWAY	Leukocyte transendothelial migration	0.007889946	CXCL12;CXCR4

Figure 6. KEGG and GO pathways of Hub Genes.

Table I. Biological, cellular and molecular enrichment pathways.

Category	Term	Description	Count	FDR
BP	GO:0030198	Extracellular matrix organization	22	5.28E-07
BP	GO:0006954	Inflammatory response	30	7.68E-07
BP	GO:0007155	Cell adhesion	32	4.01E-06
BP	GO:0008217	Regulation of blood pressure	11	8.98E-04
BP	GO:0001666	Response to hypoxia	16	0.002754706
BP	GO:0001525	Angiogenesis	18	0.003633709
BP	GO:0016337	Single organismal cell-cell adhesion	12	0.008203143
BP	GO:0070374	Positive regulation of ERK1 and ERK2 cascade	15	0.016753029
BP	GO:0071347	Cellular response to interleukin-1	10	0.0174516
BP	GO:0032496	Response to lipopolysaccharide	14	0.038385128
CC	GO:0005615	Extracellular space	64	4.63E-09
CC	GO:0005576	Extracellular region	61	1.02E-04
CC	GO:0030424	Axon	18	1.00E-03
CC	GO:0031012	Extracellular matrix	20	0.003230368
CC	GO:0048471	Perinuclear region of cytoplasm	29	0.01529324
CC	GO:0009986	Cell surface	26	0.031262473
CC	GO:0043209	Myelin sheath	13	0.031929
CC	GO:0070062	Extracellular exosome	81	0.032123168
MF	GO:0005178	Integrin binding	11	0.037757175

Biological Process (BP), Cellular Component (CC), Molecular Function (MF), False Discovery Rates (FDR).

The chemokine-mediated signalling pathway is associated with cellular migration and the control of cellular positioning at a given space and time[20,21]. Chemokines undergo signalling through heptahelical G protein-coupled receptors (GPCRs) that increase the rate of cell migration[22]. The cognate receptors of chemokines are located on the cell surfaces of GPCRs[2]. Dysregulation of chemokines is significant in the development and progression of meningiomas. GPCRs have an 80% sequence identity with different ligand selectivity for all receptors.

Positive regulation of leukocyte chemotaxis involves the mechanisms by which the chemokines draw leukocytes to the inflammation sites or infection sites[23,24]. It is a crucial immune system component that regulates immune responses in clearing damaged tissues and eliminating pathogens. Positive regulation of leukocyte chemotaxis involves the production of chemokines, expression of chemokine receptors, adhesion molecules and cytoskeletal rearrangements. The production of chemokines is enhanced by inflamed or infected tissues capable of drawing leukocytes to the infection sites[25]. The mechanism is triggered by numerous stimulants such as complementary proteins, cytokines, bacteria or viruses.

The expression of chemokine receptors occurs on the surface of leukocytes and permits them to respond to various chemokine signals[22-24]. The expression of these receptors can be down or up-regulated depending on the stimuli. We suggest that the expression of chemokine receptors is essential in leukocyte chemotaxis because leukocytes (lymphocytes, neutrophils and monocytes) express certain GPCRs on their surfaces that allow response to chemokines. For instance, pro-inflammatory cytokines such as interleukin 1 (*IL-1*) are involved in the upregulation of *CXCR4* (chemokine receptor); hence, it increases the response of the cells to *CXCL12* associated with migration of leukocytes and tissue destruction[26]. Furthermore, *IL-8* has been implicated in the upregulation of *CXCL8* on the receptor *CXCR1* on neutrophils. Hence, it increases the response of neutrophils to *CXCL8* and allows migration to the sites of infection. Thus, chemokines are involved in the upregulation of certain receptors on leukocytes.

Our study suggests that the upregulation of certain leukocyte receptors is significant in amplifying immune response to pathogens, destruction of tissues and infection in meningiomas. Therefore, by increasing the number of leukocytes responding to chemokines, the human body can effectively fight off infections and eliminate all pathogens[27]. Moreover, dysregulation of this mechanism leads to secondary infections and tissue destruction, such as arthritis.

Expressing adhesion molecules is essential in controlling leukocyte chemotaxis[28]. Adhesion molecules such as selectins or integrins express

themselves on the surface of leukocytes and adhere to the endothelial lining of blood vessels before migrating into various tissues[28-30]. At the site of tissue destruction or infection, leukocytes and chemokines increase the upregulation of adhesion molecules. An increase in the upregulation of adhesion molecules increases the capacity of leukocytes to bond to the endothelial cells before migrating into the desired tissues. Integrins are activated by the signalling of chemokines, which promotes the adherence of leukocytes to the endothelial lining and inhibits their activity. However, overexpression of adhesion molecules increases the destruction of tissues and chronic inflammations, leading to secondary infections such as asthma or inflammatory bowels.

Our study proposes that the migration of leukocytes in meningiomas is coupled with a complex chain of cytoskeletal rearrangements that permits the movement of leukocytes into the tumor sites[31,32]. The human cytoskeleton is a network of protein filaments that offers structural support to tissues, organs and cells, allowing them to maintain their original shape and size[31]. In the event of migration of leukocytes, the human cytoskeleton is altered and rearranged to permit the movement of cells into the infection sites. The mechanism of cytoskeletal rearrangement is a complex multi-process that incorporates numerous signalling molecules and critical regulators such as Rac and Rho (GTPases)[33,34]. Rac and Rho are molecular switches that turn on and off numerous signalling pathways associated with the rearrangement of the cytoskeleton.

In meningioma, leukocytes are loaded onto the benign tumors, where they improve the immune response against the growth and development of the tumors. We propose that the molecular mechanisms involved in the migration of leukocytes and rearrangement of the cytoskeleton could be targeted as new therapeutic targets in diagnosing and treating meningiomas.

The second messenger-mediated signalling pathway was critical in regulating biological processes involved in the growth and development of meningioma. An aberrant activation of the second messenger-mediated signalling pathway has been implicated in the progression of meningioma through the cyclic AMP pathway (cAMP)[35,36]. In the cAMP pathway, the hormones and neurotransmitters (extracellular signals) adhere to the GPCRs on the cell surfaces and activate adenylate cyclase, responsible for cAMP production from ATP. After that, cAMP activates the protein kinase A that controls various signalling cascades downstream.

Previous studies[37,38] have proposed that aberrant activation of protein kinase A increases cell proliferation and survival in meningioma. Furthermore, cAMP activation increases the invasion and metastasis rate in meningioma[35,36]. We observed that stimulation of the calcium signalling pathway led to an influx of calcium ions into the cells, enhancing cellular migration and proliferation. Understanding the molecular mechanisms of second messenger-mediated signalling in meningioma may provide insights into new therapeutic targets for treating this disease.

The chemokine signalling pathway involves a complicated network of intracellular patterns producing chemokines, receptor expression and numerous cellular responses[39]. In meningeal carcinoma, chemokines are manufactured by the infiltrating immune cells recruited into the tumor microenvironment. Hence, the chemokine signalling pathway is often dysregulated in meningeal carcinoma. Particularly, the overexpression of chemokines and their receptors (*CXCL12*, *CXCR4*, *CXCR7* and *CXCL2*) has been observed in meningioma tissues compared to healthy tissues. These chemokines and their receptors are often involved in adding leukocytes into the tumor microenvironment, enhancing meningeal carcinoma's growth and development.

The nuclear factor kappa B (*NF-κB*) pathway is essential in controlling various biological processes, such as the survival of cells' inflammatory and immune responses[40,41]. We propose that a dysregulation of this pathway is crucial in cancer development. In normal tissues, *NF-κB* is inactivated and bound to the I-kappa B (inhibitors); however, it is activated in the presence of oxidative stress markers or inflammatory cytokines and consequently, I-kappa B is destroyed, allowing the translocation of *NF-κB* to the nucleus. Once in the nucleus, *NF-κB* binds to DNA sequences and controls the expression of various genes.

We suggest that in meningioma, activation of the *NF-κB* pathway increases the growth and development of tumors. Moreover, previous studies[40,41] suggested that *NF-κB* is involved in cell proliferation, migration and survival. The pathway plays a key role in producing pro-inflammatory cytokines that increase the recruitment of immune cells linked with the progression of meningeal carcinoma. We propose that targeting this pathway

could lead to a significant therapeutic discovery in diagnosing and treating meningeal carcinoma. Inhibiting its activation is responsible for introducing apoptosis and sensitizing cells to adjuvant and neoadjuvant chemotherapy. Therefore, dysregulation of this pathway is crucial in the growth and development of meningeal carcinoma.

The cytokine-cytokine receptor interactions pathway regulate the immune system and signalling of various cell molecules[42,43]. Cytokines bind to various cytokine receptors and initiate a downstream signalling cascade of cell proliferation, cell differentiation and cell survival[42]. The dysregulation of cytokines such as interleukins (IL-6, *IL-10* and *IL-8*) and their corresponding receptors are critical in regulating meningeal carcinoma. The upregulation of these interleukins increases the tumor invasion and metastasis rate, increasing the grade and level of meningioma.

Additionally, cytokine-cytokine receptor dysregulation is critical in meningeal carcinoma's pathogenesis. Specifically, *CXCR2,* a receptor of *CXCL2,* is commonly expressed in meningioma cells compared to healthy cells, where it has a role in cellular invasion and migration. Therefore, we propose that a dysregulation of these interactions could be targeted to discover novel treatments for meningioma. Clinical experiments have proved that inhibiting the action of IL-6 through monoclonal antibodies is critical in inhibiting the growth and progression of meningeal carcinoma[44].

Our study suggests that the leukocyte transendothelial migration (LTEM) pathway is a complicated pathway involving the migration of leukocytes across the endothelial barrier into the tissues and cells in response to pathogens[45]. In meningioma, dysregulation of LTEM increases the capacity of tumor cells to generate chemoattractants and chemokines that enhance the infiltration of leukocytes into the microenvironments. The recruitment of leukocytes into the microenvironment enhances angiogenesis and proliferation of tumors. LTEM involves rolling leukocytes along the endothelial lining, activating integrins, and adherence to the endothelial lining using molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cellular adhesion molecule-1 (VCAM-1) and E-selectin before transmigration across the barrier.

We identified five overlapping hub genes (*CXCL8*, *AGT*, *CXCR4*, *CXCL12* and *CXCL2*) implicated in meningeal carcinoma's growth and development. In meningeal carcinoma, *CXCL8* is overexpressed in tumor cells, which is thought to contribute to tumor progression and immune evasion. *CXCL8* can promote tumor cell proliferation and angiogenesis, as well as inhibit the immune response by recruiting myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) to the tumor microenvironment[46].

Our study established that the angiotensinogen (*AGT*) gene encodes the precursor protein for angiotensin peptides, which are crucial in regulating blood pressure and electrolyte balance. *AGT* is often overexpressed in meningioma tissues compared to normal tissues; therefore, it increases the rate of cell proliferation and invasion and the overall resistance to chemotherapy[47]. The expression of *AGT* is dependent on factors such as hypoxia-inducible factors (HIFs) that increase its levels by activating the P13K/AKT pathways. Additionally, components of *AGT,* such as the renin-angiotensin system (RAS), have a crucial role in promoting angiogenesis and the development of edema. RAS enhances angiogenesis by activating the vascular endothelial growth factor (*VEGF*). *VEGF* increases the vascular system's permeability, increasing the growth and development of edema.

Our study observed that C-X-C chemokine receptor type 4 (*CXCR4*) is a gene that encodes a chemokine receptor protein, which regulates cell migration and proliferation. *CXCR4* is often elevated in meningeal carcinoma compared to healthy samples. It has a role in controlling the movement of leukocytes and transmigration across the blood-brain barrier[48]. *CXCR4* interacts with its ligand *CXCL12* to increase its expression in the tumor microenvironment. The interaction between *CXCR4* and *CXCL12* activates the MAPK pathway that exacerbates cell proliferation, migration and survival.

Targeting *CXCR4* and its downstream signaling pathways may represent a potential therapeutic strategy for treating meningeal carcinoma. Inhibitors of *CXCR4* have been shown to decrease tumor growth and metastasis in various cancer models, including meningeal carcinoma. However, further research is needed to fully understand the role of *CXCR4* in developing and progressing this disease and to evaluate the efficacy and safety of *CXCR4* inhibitors in clinical settings.

Conclusions

Our main objective was to identify five hub genes (*CXCL8*, *AGT*, *CXCR4*, *CXCL12,* and *CXCL2*) essential in meningeal carcinoma's growth

and development. These hub genes were important molecules in the pathogenesis of meningeal carcinoma, promoting tumor progression, immune evasion, and the development of tumor-associated edema. We established that the DEGs were enriched in biological pathways of chemokine-mediated signaling, positive regulation of leukocyte chemotaxis, second messenger-mediated signaling, induction of positive chemotaxis, *CXCR* chemokine receptor binding and activities of cytokines.

The significant KEGG pathways were the chemokine signaling pathway, NF-kappa B signaling pathway, cytokine-cytokine receptor interactions, pathways in cancer, human cytomegalovirus infection, leukocyte transendothelial migration, and intestinal immune network for the production of IgA. Our findings suggest that these hub genes and pathways could be targeted in clinical research to discover new treatments for meningeal carcinoma.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval and Informed Consent
Not applicable.

Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

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Not applicable.

Authors' Contribution
JL, YZ, KXB, XJQ, YZ, and HB participated in the draft and design, supervision and editing, resources, original draft writing, experimental implementation, and data statistics and analysis. All authors read and approved the final manuscript.

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