Meningiomas and Proteomics: Focus on New Potential Biomarkers and Molecular Pathways

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Abstract. *Meningiomas are one of the most common tumors affecting the central nervous system, exhibiting a great heterogeneity in grading, treatment and molecular background. This article provides an overview of the current literature regarding the molecular aspect of meningiomas. Analysis of potential biomarkers in serum, cerebrospinal fluid (CSF) and pathological tissues was reported. Applying bioinformatic methods and matching the common proteic profile, arising from different biological samples, we highlighted the role of nine proteins, particularly related to tumorigenesis and grading of meningiomas: serpin peptidase inhibitor alpha 1, ceruloplasmin, hemopexin, albumin, C3, apolipoprotein, haptoglobin, amyloid-P-component serum and alpha-1-beta-glycoprotein. These proteins and their associated pathways, including complement and coagulation cascades, plasma lipoprotein particle remodeling and lipid metabolism could be considered possible diagnostic, prognostic biomarkers, and eventually therapeutic targets. Further investigations are needed to better characterize the role of these proteins and pathways in meningiomas. The role of new therapeutic strategies are also discussed.*

Meningiomas account for approximately 20% of all intracranial tumors in males and 38% in females (1, 2). They arise from arachnoidal cells of the leptomeninges and may occur in different sites. The current World Health Organization (WHO) classification involves several variants or subtypes, divided into three grades (WHO I, II, III) (3, 4). Depending on the location and WHO grading, treatment options include surgery and postoperative radiation therapy with stereotactic radiosurgery and fractionated external beam radiation therapy (5). Even though meningiomas are generally benign, higher-grade tumors demonstrate a tendency to progress and recur (6). Heterogeneity in genetic, molecular and morphological features leads to difficulties in management (7, 8). Tumorigenesis and tumor progression in meningiomas are related to mutations or alterations of tumor-suppressor genes and loss of heterozygosity of different chromosomes (9-12). Common genetic alterations are the monosomy of chromosome 22, observed in about the 70% of meningiomas (13-15), and mutations of tumor suppressor neurofibromatosis type 2 (NF2) associated with over 60% of sporadic meningiomas (16-19). Progression and recurrence of meningiomas is associated with deregulation of several genes such as histone cluster 1 (6p) (20), tissue inhibitor metalloproteinases (TIMPs) (21-23), and WNT signaling pathway (24), as well as loss of heterozygosity of DAL1, a member of the 4.1 superfamily (25, 26) Atypical meningiomas show chromosomal losses of 1p, 6q, 10, 14q, and 18q, as well as multiple chromosomal gains (27-29). Moreover, several reports have demonstrated the association of single nucleotide polymorphism (SNPs) and epigenetic aberrations with a higher risk for developing meningiomas (30-34). Proteomic analysis is a relatively new procedure which is highly informative for the identification of potential surrogate markers in different types of brain tumor (35, 36).

Proteins and Their Related Pathways

Tissue samples. Recent articles reported a panel of proteins, such as integrin, WNT, RAS, fibroblast growth factor (FGF), epidermal growth factor (EGF), exhibiting a different expression profile within different grades of meningioma, which are implicated in the modulation of essential signal transduction of apoptosis and ubiquitin proteasome signaling in meningioma (37-39). Integrin alpha beta 5 and alpha beta 3 seemed to be strictly

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associated with meningioma pathogenesis (40). Thus, integrin beta 5, vasodilator-stimulated phosphoprotein, collagen alpha-3 (VI) chain, and filamin-A were found to be up-regulated in benign meningiomas. The signal-transducing component of the WNT receptor was down-regulated in benign and atypical meningiomas, except guanine nucleotide-binding protein subunit gamma-12, which was slightly up-regulated in all different grades of meningiomas (41-43). RAS-related protein R-RAS2, RAS-related C3 botulinum toxin substrate 2 were found to be associated with the EGFR pathway and represent the main part of the FGF signaling, integrin signaling and RAS pathways involved in tumor development. Neuroblast differentiation-associated protein (AHNK), protein S100-A6 and protein S100-A10 interact and mediate different key cellular processes (44, 45) and are significantly up-regulated in benign and anaplastic meningiomas. In addition, elevated expression levels of tissue proteins such as caveolin, complement factor B, Y box protein, vinculin, Src homology 2 domain containing binding protein 1 and guanine nucleotide-binding protein G(i) subunit alpha were detected in benign and anaplastic meningiomas. Proteins such as serine/threonine-protein phosphatase 2B and tubulin alpha-1C chain appeared to be down-regulated in different grades of meningiomas. Apolipoprotein E (APO E), serum albumin, apolipoprotein A-I, alpha-1 antitrypsin, galectin-3, vimentin, endoplasmin, annexin A2, glutathione S-transferase P, profilin were reported differently expressed in human meningiomas (46, 47). Phosphorylated vimentin was proposed as a discriminative marker for non-infiltrative and non-invasive meningiomas (48). New candidates such as gelsolin, galectin-3, neuromodulin and tumor protein D54 were found to be expressed in benign and anaplastic meningiomas.

Cerebrospinal fluid (CSF). Human CSF has been used as a significant source for protein biomarker studies (49). Recently, Kim *et al*. identified a small number of proteins in CSF of patients suffering from meningiomas (50). Seven spots were found for secreted proteins expressed at high levels in the majority of CSF of samples from patients with meningioma, and for three proteins expressed at lower levels (50). In greater detail, it has been reported that the content of APO E, APO J and alpha-1-antitrypsin (A1AT) was found to be increased compared to controls, while prostaglandin D2 synthase (PTGDS), transthyretin precursor (TTR) and beta 2 macroglobulin (B2M) was found to be decreased. APO E has been detected in normal human brain tissue and in human intracranial neoplasm (51). On the other hand, APO J is a major carrier protein of soluble circulating amyloid B in body fluids; it may keep the peptide in a soluble form and is considered to have an anti-amyloidogenic effect (52).

Serum. Proteomic analysis of serum from patients with different grades of meningioma identified proteins such as vimentin, alpha-2-macroglobulin, APO B and APO A-I and antithrombin-III, which exhibited a sequential enhancement in increasing grade of malignancy of meningiomas, and were also proposed as potential predictive markers (36). Enhanced levels of a few important candidates involved in the coagulation system and hemostasis, including antithrombin-III, alpha-2-antiplasmin, vitamin K-dependent protein S, fibrinogen alpha chain, plasminogen, alpha-2-macroglobulin and coagulation factor XII, were found in different grades of meningioma. In addition, the activation of complement cascades has been demonstrated in meningiomas, with up-regulation of few complement factors including C5, C8 beta chain, C6, and C4-B. The role of complement proteins in cancer growth is still unknown, but is likely related to dysregulation of mitogenic signaling pathways, constant cellular proliferation, angiogenesis, resistance to apoptosis, and escape from the immune system (53, 57). APO A-I and A-II, alpha-1-acid glycoprotein 2, hemoglobin subunit beta/alpha, leucine-rich alpha-2-glycoprotein and vimentin exhibited high expression levels in meningiomas. However, isoforms of APO A-I and A-II have also been reported as potential markers for other cancer types such as ovarian and prostatic (54, 55). Expression levels of other serum proteins, including thrombispondin-I, serotransferrin, and alpha-2-macroglobulin, were found to be altered in patients with meningioma. Some of these identified proteins, such as APO E, carbonic anhydrase 1, leucine-rich a-2-glycoprotein and afamin, which showed alteration in expression levels in benign meningiomas (WHO I), may act as potential candidate markers for meningioma at their early stages of development. Different proteins such as vimentin, α-2-macroglobulin, APO B, APO A-I and antithrombin-III, which exhibited alterations in expression levels between benign, atypical or anaplastic meningiomas, can be considered as potential disease-monitoring markers.

This review aimed to evaluate the current findings regarding proteomic analysis in human meningioma, the pathways involved in tumorigenesis, and finally the common profiles derived from different samples, in order to suggest possible diagnostic and prognostic markers, and postulate potential therapeutic targets.

Materials and Methods

Data collection. A PubMed literature search including the last 10 years of all English-language publications reporting proteomic analysis and functional pathways in meningiomas was performed. Terms used in the research were "Meningioma" in multiple combinations with "proteomics", "tissue proteomics", "serum proteomics" and "cerebrospinal fluid proteomics". A total of 11 articles were retrieved and reviewed, and a total of 153 non-redundant proteins were extracted. Reports were tabulated by

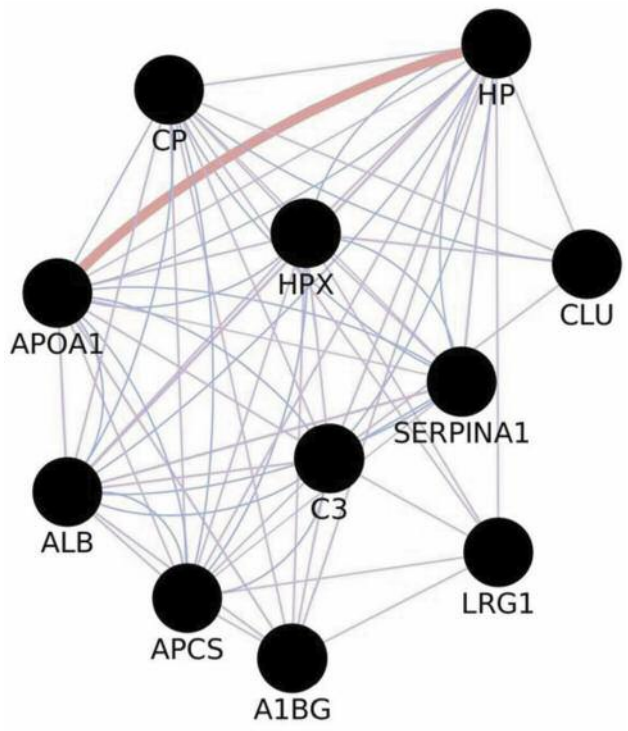

Figure 1. *Associated proteins in meningiomas, depicted as circular nodes, extracted after merging networks derived from in-gel proteomics with those from gel-free proteomics. Edges: Co-expression (violet), co-localization (light blue) and physical interactions (pink).*

proteomic findings in brain tissue, CSF and serum. All proteins and genes which were significantly differently expressed (up-regulated, or down-regulated) in meningioma tissues, serum or CSF compared to controls were selected. A minimal fold-change of 1.5 for univocal comparison of the same genes/proteins between different studies was considered. Selected genes/proteins were divided into two study groups: a gel-proteomics group, including all deregulated proteins arising from multiple substrates and obtained by gel-proteomic methods; and a gel-free proteomics group, collecting all the proteins which appeared to be deregulated from gel-free screening methods.

Protein interaction network construction. All these molecules were searched through the GeneMANIA Human Database (http://www.genemania.org), in order to find relationships and enrich their interaction networks with new potential partners. GeneMANIA is a web tool useful for generating hypotheses about gene function, for building gene networks, and for prioritizing genes in functional assays. Cytoscape is an open-source software platform for visualizing molecular interactions and biological pathways. In GeneMANIA networks, genes are depicted as circular nodes and their interactions by edges of different shape and colors. Edge colors and shapes reflect the type and the strength of interactions. We identified two major networks, gel-proteomic network and gel-free proteomic network, using as query genes or proteins arising from the two groups considered. GeneMANIA's default settings were initially modified to search relationships among the components of each query list without related genes, using pathway, co-localization, co-expression, physical interaction and similar protein domain as attributes. Gel-proteomic network and gel-free proteomic network were subsequently merged by intersection, in order to determine and maintain only the shared molecules for the further analysis. Proteins highlighted by the merging process were then resubmitted to GeneMANIA to expand their interaction network with new potential partners. GeneMANIA's options were set according to a maximum of 40 related genes, using the same attributes described previously.

Cluster and functional analysis. The resulting network was analyzed by Molecular Complex DEtection (MCODE) clustering tool (http://apps.cytoscape.org/apps/mcode) to find highly interconnected clusters in a network. Default MCODE parameters were used on the whole network to allow the extraction of clusters containing almost all proteins obtained from the merging process. Small clusters were discarded and the largest clusters, with the highest score, were submitted to ClueGo (http://apps.cytoscape.org/apps/cluego). By selecting "GO-terms fusion", terms with similar associated genes (by Gene Ontology) were fused in order to minimize redundancy. The options "Detailed Network" and K-value 0.45, respectively, were used to obtain specific GO-terms with few associated genes and high percentage of significance of the uploaded genes, increasing association strength between GO-terms and genes.

Results

A total of 153 non-redundant proteins in meningiomas, arising from our reviewed articles, were analyzed. Results obtained by merging gel-free proteomic data and in-gel proteomic data, revealed 11 proteins common to both approaches and detected in all samples considered: serpin peptidase inhibitor alpha 1 (SERPINA1), ceruloplasmin (CP), hemopexin (HPX), albumin (ALB), complement component 3 (C3), apolipoprotein A1 (APO A1), haptoglobin (HP), amyloid-P-component serum (APCS) and alpha-1-beta-glycoprotein (A1BG), clusterin (CLU), leucine-rich alpha-2-glycoprotein 1 (LRG1) (Figure 1). Gene-enrichment by GeneMANIA allowed the expansion of original network to 111 nodes and 6,410 unique edges (Figure 2). Nodes indicate the proteins from the original dataset and those directly interacting with them, while edges, of different shape and color, represent the specific type of interaction (*e.g.* co-expression, and co-localization). By MCODE analysis, a large cluster of 92 nodes and 5,483 unique edges, with a score of 82,901, was extracted from the enriched network (Figure 3). Another potential cluster, comprising 10 nodes and 15 edges, was discarded due to its low score value (score=2,889).

After gene enrichment and cluster analysis, this list was further reduced to nine proteins still present in the cluster of 92 nodes, with exclusion of CLU and LRG1 because of their lack of interactions. All these molecules seem to be apparently highly interconnected with each other by edges, indicating coexpression and co-localization. Functional analysis using ClueGO (http://apps.cytoscape.org/ apps/cluego), followed by removal of redundant terms, showed a significant association

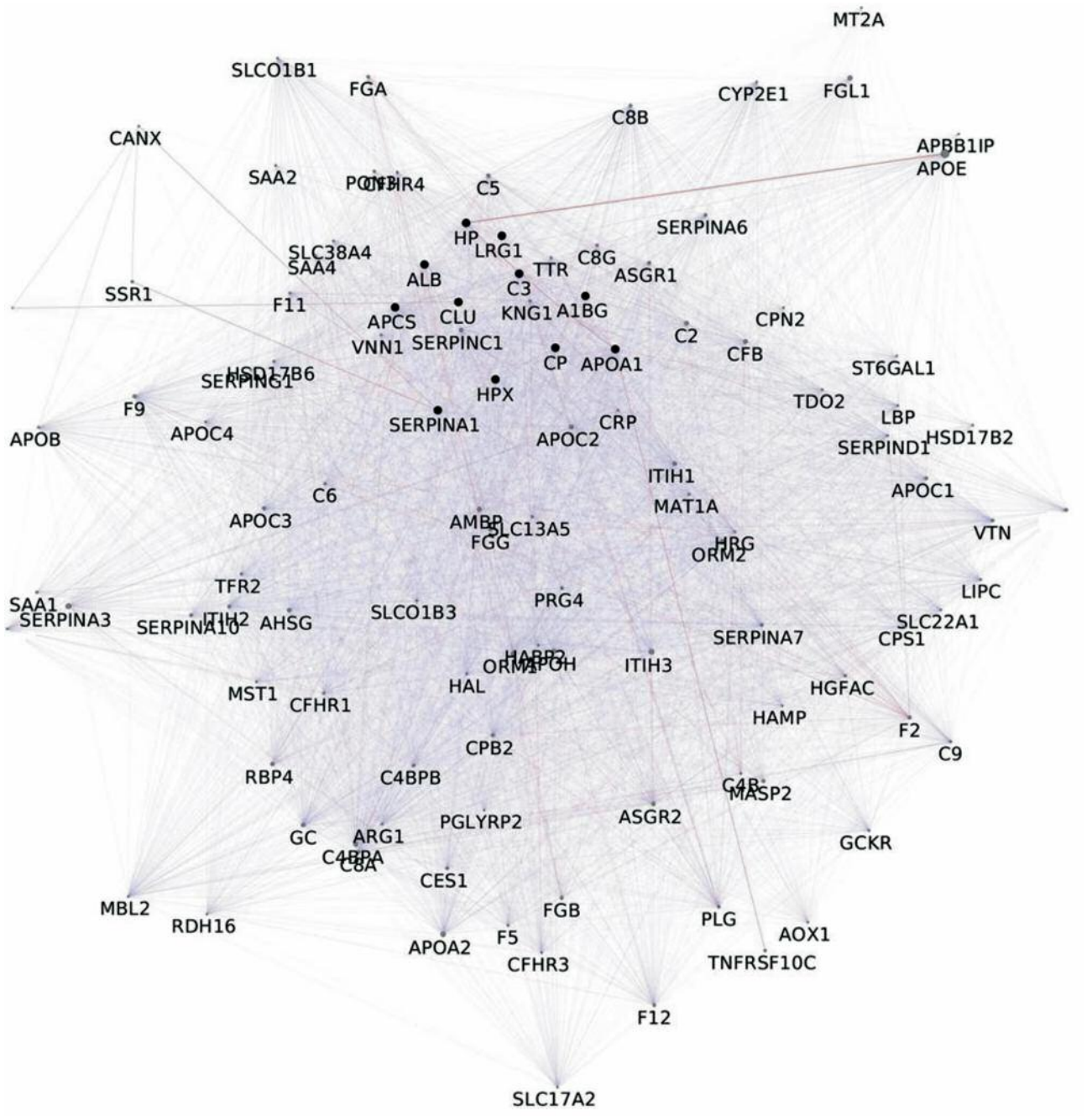

Figure 2. *Network arising after gene enrichment on proteins common to both in-gel proteomics and gel-free proteomics of meningiomas. Query genes/proteins are represented by black nodes, newly found interacting partners are depicted as grey nodes.*

(pV≤0.05, k-value=0.45) of the 92-node cluster with the following Gene-Ontology terms: amyloids, complement and coagulation cascades, complement cascade, initial triggering of complement, transport of organic anions, fibrinolysis, glycosaminoglycan binding, killing of cells in other organism involved in symbiotic interaction, lipid localization, organic hydroxyl compound transport, plasma lipoprotein particle remodeling, positive regulation of humoral immune response, regulation of protein processing, regulation of response to external stimulus. Genes associated with each functional group are reported in the Table I. A detailed graphical overview of ClueGO results is reported in Figures 4 and 5.

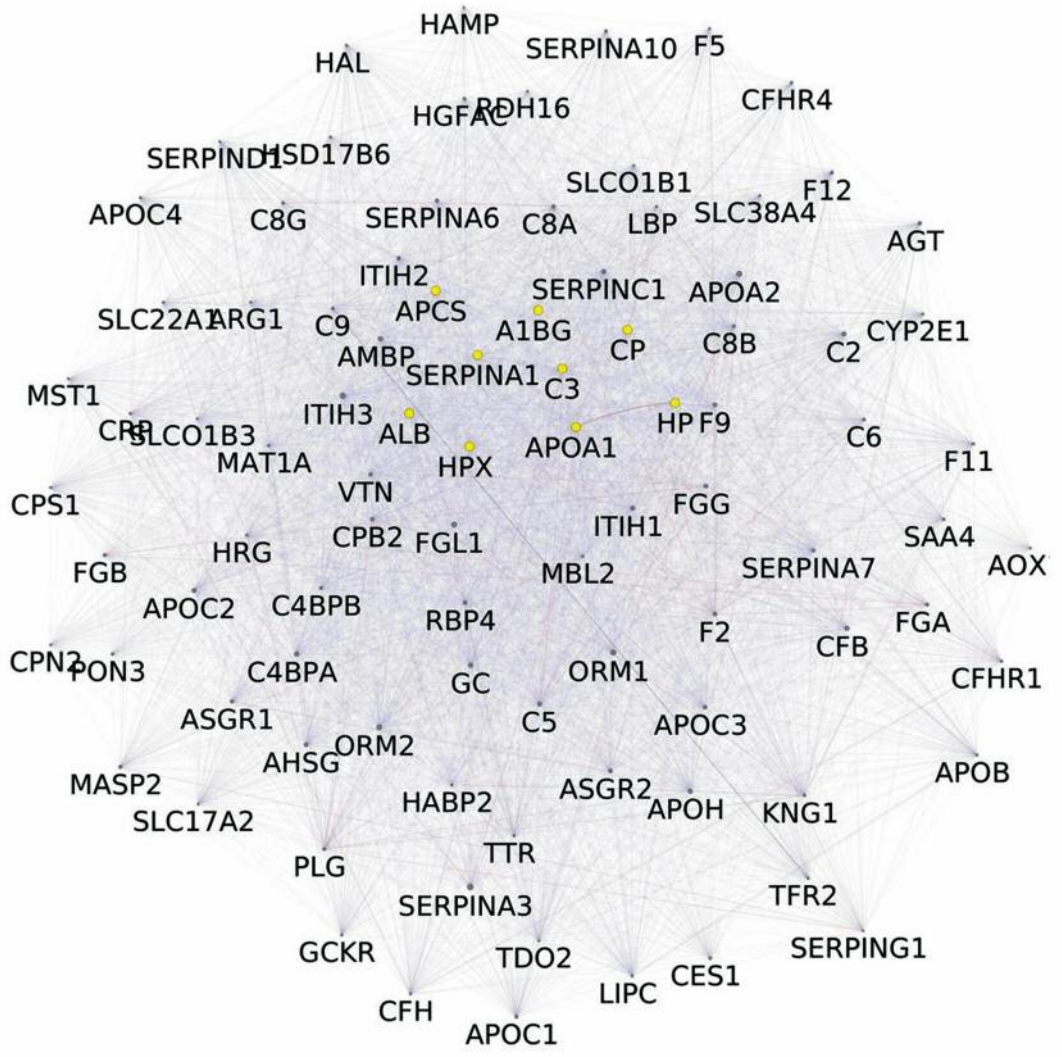

Figure 3. *Cluster arising from the enriched network reported in Figure 2. The original dataset is reduced to nine proteins highlighted in yellow.*

Discussion

The proteomic characterization of different grades of meningioma, through a bioinformatic approach, offers the possibility of investigating their molecular hetereogeneity. Few previous studies, focusing on the analysis of various biological samples, have been conducted to explore the protein spectrum of different grades of these tumors and its correlation with functional pathways, in order to find potential prognostic and therapeutic biomarkers (46, 50, 56, 57). Our analysis highlighted the dysregulation of nine proteins in all samples considered: SERPINA1, CP, HPX, APOA1, ALB, C3, HP, APCS and A1BG belonging to the pathways which showed major involvement in meningioma development and progression, plasma complement/coagulation cascades and lipoprotein particle remodeling (58, 59).

Several studies have demonstrated that the activation of the coagulation cascade is implicated in tumor development, however, the exact mechanism(s) by which coagulation proteins promote tumorigenesis are not fully understood, and are likely related to peritumoral deposition of fibrin and to the alteration of hemostatic factors, hence favoring proliferation, angiogenesis and metastasis (58, 60-62). Serine proteinases are capable of degrading the extracellular matrix (ECM) and basement membranes and have been implicated in human brain tumors, playing a decisive role in this malignant process by degradation of brain ECM components, secreting adhesion molecules, regulating the activity of growth and chemotactic factors and providing space for movement and infiltration (63). In detail, expression of SERPINA1, an inhibitor of serine proteases, was found to be enhanced from benign to anaplastic meningioma, suggesting

Table I. *ClueGO functional groups with associated genes.*

Function	Genes
Amyloids	*APCS, APOA1, FGA, TTR*
Complement and coagulation cascades	*AGT, AHSG, AOX1, APCS, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOH, ARG1, C3, C4BPA, C4BPB, C5, C6, C8A, C8B, C8G, C9, CFB, CFH, CFHR1, CFHR4, CPB2, CRP, F11, F12, F2, F9, FGA, FGG, HP, HPX, HRG, LBP, LIPC, MASP2, MBL2, ORM1, ORM2, PLG, RBP4, SAA4, SERPINA1, SERPINA10, SERPINA3, SERPINA6, SERPINA7, SERPINC1, SERPIND1, SERPING1*
Complement cascade	*AHSG, APOA1, APOB, C3, C4BPA, C4BPB, C5, C6, C8A, C8B, C8G, C9, CFB, CFH, CRP, FGG, MASP2, MBL2, PLG, SERPING1*
Initial triggering of complement	*AGT, AHSG, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOH, C3, CFB, CFHR4, CRP, LBP, LIPC, MASP2, MBL2, RBP4*
Transport of organic anions	*ALB, SLC22A1, SLCO1B1, SLCO1B3*
Fibrinolysis	*AGT, AHSG, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOH, C3, C4BPA, C4BPB, C5, C6, C8A, C8B, C8G, C9, CFB, CFH, CFHR4, CPB2, CRP, F11, F12, F2, HRG, LBP, LIPC, PLG, RBP4, SERPINC1, SERPING1*
Glycosaminoglycan binding	*APOB, APOH, CFH, F11, HABP2, HRG, LIPC, SERPINA10, SERPINC1, SERPIND1*
Killing of cells involved in symbiotic interaction	*ALB, C9, MBL2*
Lipid localization	*AGT, AHSG, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOH, C3, CFB, CFHR4, CRP, LBP, LIPC, MASP2, MBL2, RBP4*
Organic hydroxy compound transport	*AGT, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, ARG1, C5, LIPC, SLC22A1*
Plasma lipoprotein particle remodeling	*AGT, AHSG, ALB, AMBP, APOA1, APOA2, APOB, APOC1, APOC2, APOC3, APOH, ARG1, ASGR1, ASGR2, C3, C5, CFHR4, CPB2, CPS1, CRP, CYP2E1, F11, F12, F2, GC, GCKR, HP, HPX, HRG, HSD17B6, LBP, LIPC, MBL2, PLG, RBP4, SERPINA6, SERPING1, SLC22A1, SLCO1B1, SLCO1B3, TFR2, TTR*
Positive regulation of humoral immune response	*C3, C6, HPX*
Regulation of protein processing	*AGT, AHSG, AMBP, APOA1, APOA2, APOC1, APOC3, C3, C4BPA, C4BPB, C5, C6, C8A, C8B, C8G, C9, CFB, CFH, CPB2, F12, F2, HRG, ITIH1, ITIH2, ITIH3, SERPINA1, SERPINA10, SERPINA3, SERPINA6, SERPINA7, SERPINC1, SERPIND1, SERPING1*
Regulation of response to external stimulus	*AGT, AHSG, ALB, APOA1, APOA2, APOC1, APOC2, APOC3, APOH, C3, C4BPA, C4BPB, C5, C6, C8A, C8B, C8G, C9, CFB, CFH, CPB2, F11, F12, F2, F9, FGA, FGG, HABP2, HGFAC, HP, HRG, LBP, MASP2, MST1, PLG, RBP4, SERPINA1, SERPINC1, SERPING1*

its role as prognostic biomarker (64-68). Overexpression of SERPINA1 has been associated with the invasive and metastatic behavior in lung, colorectal, and gastric carcinoma (64-68). In our analysis, the significant association between higher SERPINA1 levels and meningioma grade suggests a possible role of this protein as a therapeutic target for monoclonal antibodies, in order to limit ECM degradation and infiltrative behavior, similarly to the mechanism of antiangiogenetic therapy with monoclonal antibodies to vascular endothelial growth factor in meningioma treatment (69). Further development of targeted therapies designed to inhibit tumor infiltration, and to evaluate these new agents in clinical trials, will be needed to improve survival and quality of life for patients with brain tumors (70).

Moreover, increased levels of ceruloplasmin have also been reported in different types of cancers, such as ovarian, breast, renal, colonic and brain, as well as in cancers stem-like cells of glioblastoma multiforme (71). Accordingly, in our analysis, expression of ceruloplasmin was found to be enhanced from low to higher grade meningioma. However, little is known on the role of this protein in cancerogenesis and its potential application in anticancer drug development (72, 73).

The complement cascade represents the other pathway involved in tumorigenesis and progression of meningiomas emerging from our review. The reviewed articles, through comparative bioinformatic proteomic approaches, supported the activation of complement pathway in meningioma development, probably due to its role in cellular proliferation and regeneration. The exact mechanism through which complement proteins influence cancer growth is still unknown, but dysregulation of mitogenic signaling pathways, constant cellular proliferation, angiogenesis, resistance to apoptosis, and escape from the immune-system have been postulated (53). Bouwens *et al.* investigated the involvement of the three complement cascade-initiating pathways and their consequences in terms of complement pathway continuation in glioblastoma multiforme by determining preoperative serum levels and tissue localizations of C1q, mannose binding lectin (MBL), factor B, as well as of C3 and C5b-9 (74). The three initiating pathways of the complement system converge at the

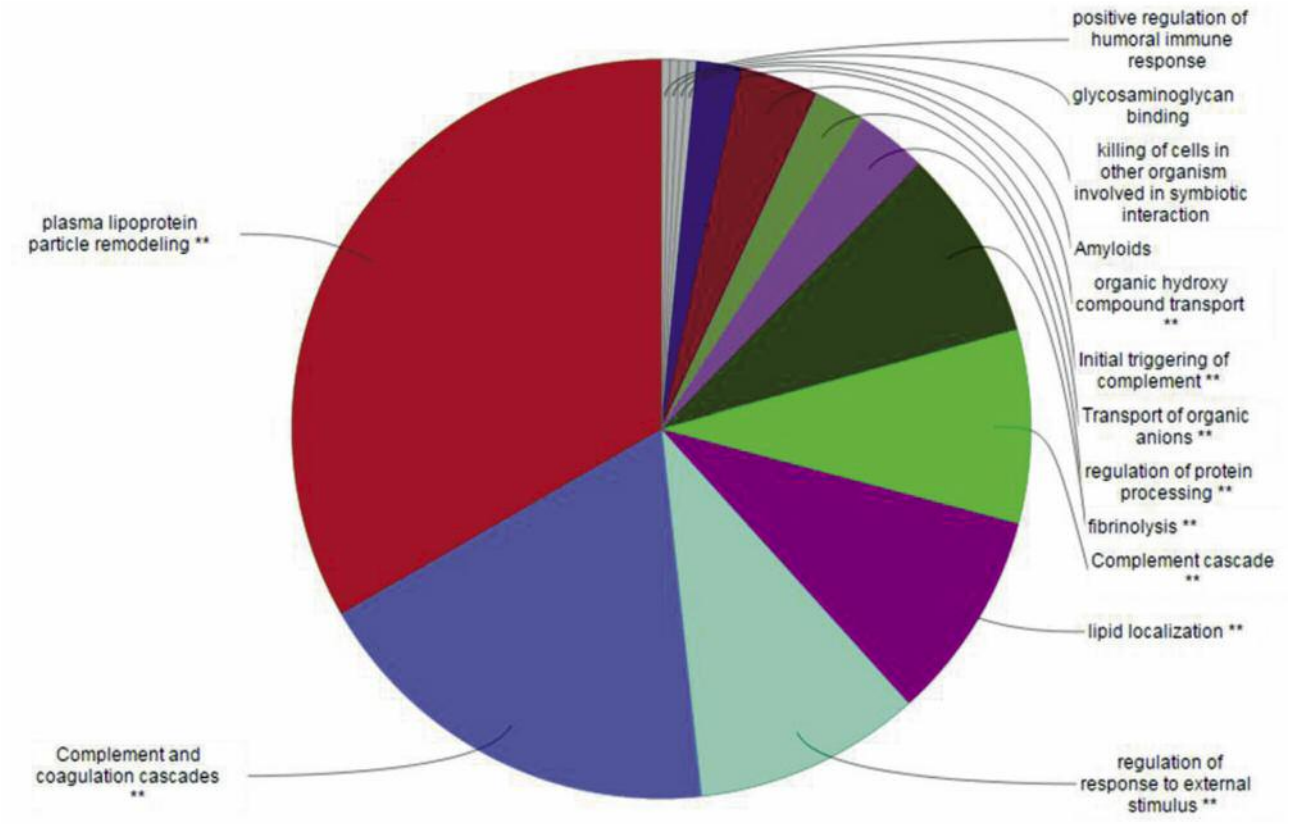

Figure 4. *ClueGO pie chart of principal Gene-Ontology (GO) functions associated to the 92 node cluster. In order to avoid redundancy, functions reported in the pie chart are those with the highest numbers of related genes. **Indicates significant association between the 92 node cluster and represented GO terms (pV≤0.05).*

level of proteolytic cleavage of C3 that ultimately may lead to full-blown activation of the complement cascade and to the formation of the C5b-9 complex. Consequently, the presence of C3 in tumor tissue is essential for the propagation of the complement cascade. Indeed, in our investigation, we found an enhancement of C3 levels from benign to anaplastic meningioma, supporting its role as a predictive marker. Moreover, C3 expression was found abundantly present in both necrotic and non-necrotic areas of glioblastoma multiforme tumor tissues, and C5b-9 complex was detected on individual cells in glioblastoma multiforme tumor tissue (74).

Lipid metabolism and lipoprotein particle remodeling pathway appeared particularly involved in atypical and anaplastic meningiomas (75). In the networks considered, before and after cluster analysis, one marked physical interaction was always observed regarding ALB and APOA1. Apolipoproteins are polypeptides implicated in a variety of diseases and play a significant role in diagnosis and prognosis of several conditions, especially brain tumors. APOA1, the major protein component of high-density lipoprotein, is known to play a central role in regulation of the efflux and transport of cholesterol from peripheral tissues to the liver, and as a co-factor for lecithin. Recently, Hashemi *et al*. reported the up-regulation of serum albumin, as a carrier, and APOA1 in malignant gliomas, reflecting the ability of both these proteins to pass into the interstitium of malignant glioma because of either the disruption of the brain–blood barrier or its absence in tumor capillaries, and suggesting its major involvement in the vascular microenvironment, tumor development, migration and angiogenesis (76). Regarding meningioma, Sharma *et al*. reported an up-regulation of both albumin and APOA1 increasing from benign to anaplastic meningioma, due to the same mechanism of alteration of the brain–blood barrier (77). Current evidence also suggests the involvement of APOA1 as a promising diagnostic marker and a potential target for therapeutic strategies in neurodegenerative disorders. Additionally, we can postulate that these proteins and their pathways, could represent promising targets for brain cancer therapy (78, 79), strictly related to the innovative use of nanoparticles, small molecules which facilitate drug transport into the brain, with a lower rate of toxicity (80). Furthermore overexpression of HPX, HP, APCS, and A1BG was

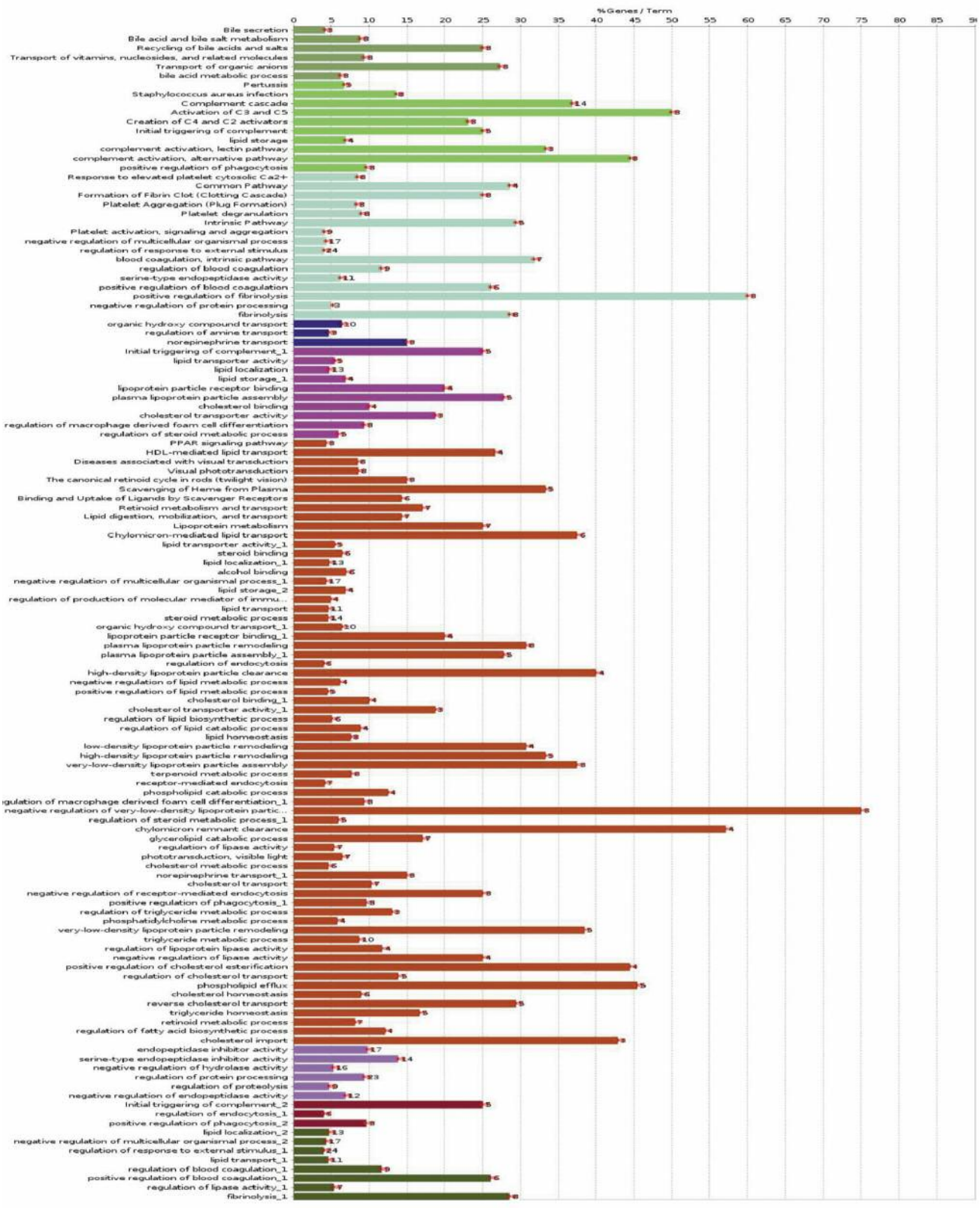

Figure 5. *Continued*

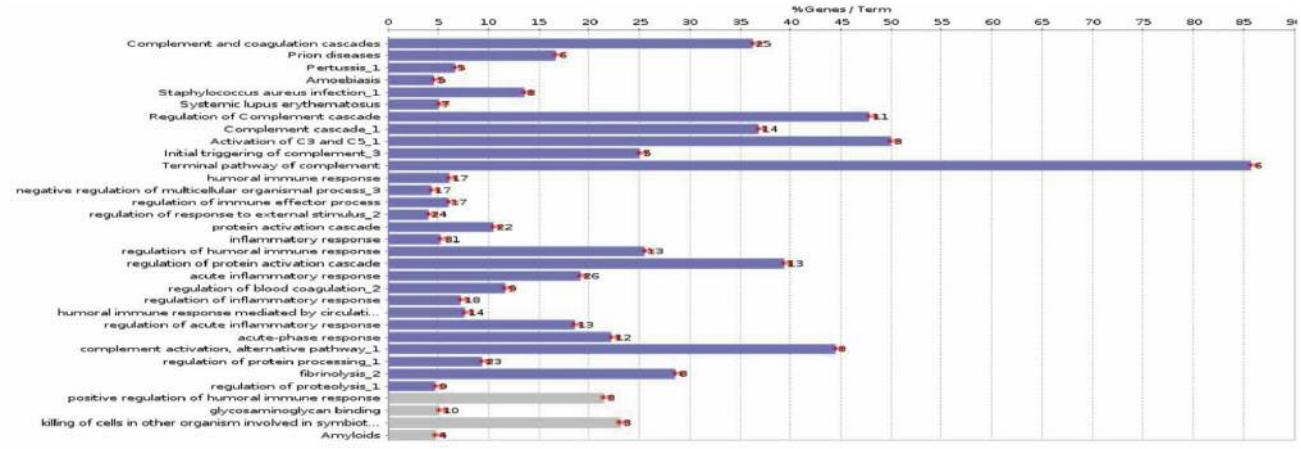

Figure 5. *Number of cluster genes associated with each Gene-Ontology function. Please refer to Figure 4 for color designations.*

demonstrated, however, the lack of relevant literature does not allow us to explain their possible role and implications in brain tumorigenesis and progression.

Conclusion

Bioinformatic methods were applied in our review of literature to identify the most common proteins and pathways leading to meningioma development and progression. The results obtained by matching genes and proteins expressed in tissues, serum and CSF samples highlighted the following proteins: SERPINA1, CP, HPX, APOA1, ALB, C3, A1BG, HP and APCS, mainly implicated in complement/coagulation cascades and pathways of lipid metabolism. Moreover, the presence of high levels of all these proteins could represent a molecular tool for prediction of clinical outcome in patients with meningioma and future targets for brain cancer therapies. Future investigations might address the study and discovery of therapies targeting these pathways at different levels in order to modify cancer behavior.

Conflicts of Interest

None to declare.

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