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Research Paper

Introducing Albumin and Interleukin 6 as Common Critical Dysregulated Proteins Between Migraine and Gliosarcoma

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ABSTRACT

Introduction: It is reported that migraine may be a risk factor for brain cancers. Since one of the best ways to assess this possible relationship is to study the molecular mechanism, here the common central dysregulated proteins between these diseases are investigated via network analysis.

Methods: The dysregulated proteins of migraine and gliosarcoma are extracted from the STRING database and interacted via Cytoscape software, version 3.7.2. to form two separate networks. Central nodes of the networks are compared to find the common central district proteins. First neighbors of the common central proteins are studied.

Results: The number of 11 hub bottlenecks was identified for each of the migraine and gliosarcoma cancer networks. Albumin (ALB) and interleukin 6 (IL6) were introduced as common differentially expressed central proteins. Kininogen 1 (KNG1), vascular endothelial growth factor A (VEGFA), and neurofibromatosis type I (NF1) the first neighbors of ALB-IL6 were connected to the central nodes of networks of the two studied diseases.

Conclusion: ALB and IL6 can be considered molecular links between migraine and brain cancers.

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Highlights

• Differentially expression of albumin (ALB) and interleukin 6 (IL6) is highlighted as the common key events in migraine and gliosarcoma.

• Kininogen 1 (KNG1), vascular endothelial growth factor A (VEGFA), and neurofibromatosis type I (NF1) are introduced as possible critical players in migraine and gliosarcoma.

• Based on four centrality parameters, ALB is characterized with stronger centrality properties relative to IL6.

Plain Language Summary

Migraine is considered as a possible risk factor for brain cancers. Therefor exploring of relationship between brain cancers and migraine is attracted attention of researchers. Understanding of diseases molecular mechanism is an important tool to better diagnosis and therapy of the studied disorders. In the present study, the common features of molecular events in migraine and gliosarcoma are studied based on protein expression changes. Analysis indicates that a few numbers of proteins play critical roles in migraine and gliosarcoma. ALB, IL6, KNG1, VEGFA, and NF1 are highlighted as the key proteins which are dysregulated in the two studied diseases. Prominent role of ALB in development of cancers is pointed out by several researchers. Important role of IL6 in promotion of migraine is disused in the previous documents. Since some diseases are risk factors for the other disorders, understanding the common features of two diseases can provide suitable therapeutic protocol to prevent development of diseases. Our finding can be used to provide suitable procedure to prevent conversion of migraine to brain cancer.

1. Introduction

Migraine is known as a public and sometimes devastating disorder (Goadsby et al., 2002). Migraine has been reported to be associated with several disorders, such as cardiovascular diseases, gastrointestinal disorders, and vertigo (Adelborg et al., 2018; Felisati et al., 2010) Documents exist about the association between migraine and the development of brain tumors (Chen et al., 2018). Several studies discussed the molecular mechanism of migraine and pointed to the genes and proteins involved in migraine development (Goadsby, 2007; Olesen et al., 1993).

Protein-protein interaction network analysis is a suitable method to assess the molecular mechanism of diseases. In this method, a set of proteins or genes involved in the evaluated disease are connected to form an interactome. Since the number of interactions and first neighbors of each protein may differ from others, the role of elements of the network is different from the other proteins. In scale-free networks, top nodes are limited by the number of first neighbors or connections to the first neighbors. These nodes are known as hubs and play a crucial role in network construction (Farahani et al., 2022; Zamanian-Azodi et al., 2021). Based on the shortest paths attributed to a node, bottleneck nodes are announced. Bottlenecks are known as central nodes of a network, which play a significant role in the integration of the network (Heidari et al., 2020). A hub node that acts as a bottleneck is known as a hub bottleneck. The hub-bottleneck nodes are powerful elements of the network and are considered critical nodes (Mateus Pellenz et al., 2022).

Hub, bottleneck, and hub-bottleneck nodes are used to detect the molecular mechanisms of many diseases (Gupta et al., 2015; Huo et al., 2017).

Data sources in network analysis can be considered databases or an experimental investigation. STRING is a well-known database that includes many diseases and related dysregulated proteins (Szklarczyk et al., 2016). In the present study, the dysregulated proteins of migraine and gliosarcoma are extracted from the STRING database and analyzed by network analysis to find central nodes that link migraine to gliosarcoma.

2. Methods and Materials

A total of 200 related proteins for migraine were searched from “the disease query” of the STRING database. The extracted proteins were interacted via undirected edges by using Cytoscpe software, version 3.7.2. The network was analyzed by “the network analyzer” application of Cytoscape software, version 3.7.2. The top

10% of nodes of the main connected component were selected as hubs and bottlenecks, respectively, based on degree value and betweenness centrality. The common hubs and bottlenecks were identified as hub bottlenecks.

As with migraine, 200 dysregulated proteins that were related to gliosarcoma were extracted from the STRING database. These proteins were interacted by Cytoscape software to form an interactome. To identify the central nodes of the network, the main connected component of the network was analyzed by "network analyzer". The hub bottlenecks were introduced as the main analyzed component.

Hub-bottleneck nodes of the two diseases were compared and the common individuals were identified. To find the critical role of the common hub bottlenecks, 10 first neighbors of each one or each set were determined from the STRING database. Finally, the common hub bottlenecks and the first neighbors were assessed and discussed.

3. Results

The retrieved proteins related to migraine were included in a network. The network included 14 isolated proteins, a subnetwork contains a pair of proteins, and a main connected component subnetwork was formed. The main connected component was constructed from 184 nodes and 2388 edges. To find the central nodes, 10% (18 proteins) of top nodes based on degree value were identified as hubs and similarly, 18 bottlenecks were determined. Among hubs and bottlenecks, 11 hub-bottleneck nodes were introduced. Table 1 presents the hub bottlenecks.

The main connected component of the gliosarcoma network was constructed from 187 nodes and 3732 undirected connections. A number of 13 proteins were isolated. Among 19 hubs and also 19 bottlenecks, 11 common hub bottlenecks were identified. Table 2 presents the list of hub-bottleneck nodes.

A comparison of Tables 1 and 2 indicates that albumin (ALB) and interleukin 6 (IL6) are the two common hub bottlenecks between migraine and gliosarcoma diseases. To better understand the role of ALB and IL6, Figures 1-3 shows 10 first neighbors of ALB, IL6, and ALB-IL6.

Table 1. List of hub bottleneck nodes of the main connected component of migraine network

No.	Display Name	Betweenness Centrality	Closeness Centrality	Degree	Stress
1	TAC1	0.036	0.612	84	18036
2	INS	0.062	0.610	78	23856
3	BDNF	0.044	0.602	72	18590
4	POMC	0.021	0.565	72	9348
5	KNG1	0.038	0.579	71	15720
6	ALB	0.034	0.592	71	16574
7	CALCA	0.027	0.570	69	13282
8	IL-6	0.019	0.574	64	11392
9	OPRM1	0.028	0.568	62	12230
10	GRM5	0.026	0.550	56	11958
11	CREB1	0.048	0.558	55	17452

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Abbreviations: ALB: Albumin; IL6: Interleukin 6; TAC1: Tachykinin precursor 1; INS, Insulin; BDNF: Brain derived neurotrophic factor; POMC: Proopiomelanocortin; KNG1: Kininogen 1; CALCA: Calcitonin related polypeptide alpha; OPRM1: Opioid receptor mu 1; GRM5: Glutamate metabotropic receptor 5; CREB1: cAMP responsive element binding protein 1.

Table 2. List of hub bottleneck nodes of the main connected component of gliosarcoma network

No.	Display Name	Betweenness Centrality	Closeness Centrality	Degree	Stress
1	TP53	0.058	0.715	117	22860
2	VEGFA	0.056	0.729	120	22588
3	ALB	0.049	0.691	108	19650
4	EGFR	0.047	0.702	114	18660
5	AKT1	0.047	0.718	118	18654
6	EGF	0.039	0.684	108	15544
7	HRAS	0.032	0.644	94	13192
8	IL6	0.022	0.667	102	12514
9	MYC	0.019	0.674	105	12424
10	ERBB2	0.016	0.653	95	9610
11	FN1	0.015	0.644	93	9342

Abbreviations: ALB: Albumin; IL6: Interleukin 6; TP53: Tumor protein p53; VEGFA: Vascular endothelial growth factor A; EGFR: Estimated glomerular filtration rate; EGF: Epidermal growth factor; FN1: Fibronectin 1.

4. Discussion

Many common features exist between diseases, especially aspects of the molecular mechanisms of diseases. Investigating common key proteins which are common between migraine and brain cancers is a way to understand migraine as a risk factor for these types of cancers. In the present study, ALB and IL6 were identified as two central common proteins which play a critical role in the protein-protein interaction networks of the two studied diseases.

Jacobsen et al investigated urinary albumin excretion as an endothelial dysfunction marker in patients with migraine (Jacobsen et al., 2013). Based on this research, no significant increase was observed in the excreted albumin level and systemic endothelial dysfunction. Therefore, they concluded that systemic endothelial dysfunction is not a prominent feature of migraine. The other document refers to low levels of serum albumin in migraine patients compared to the control group (Yazar et al., 2020).

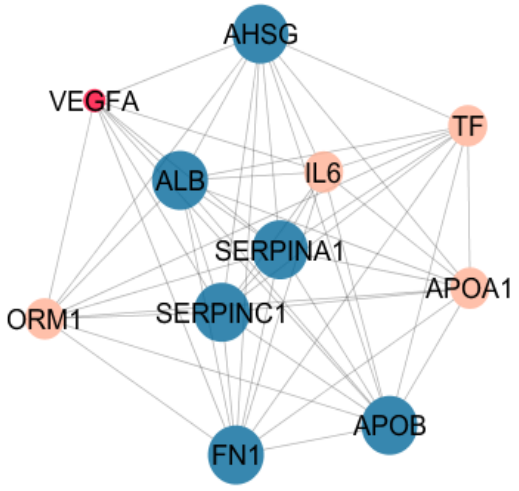

Figure 1. Albumin (ALB) and its 10 first neighbors from STRING database

Nodes are layout based on degree value.

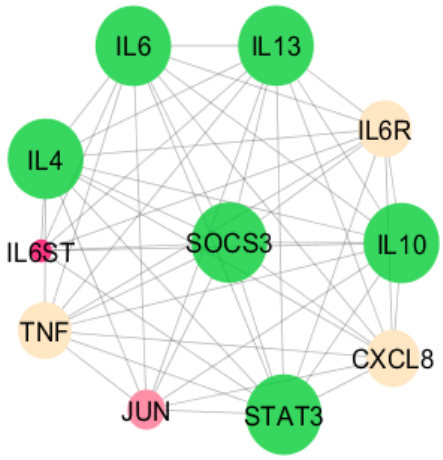

Figure 2. Interleukin 6 (IL6) and its 10 first neighbors from STRING database

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Nodes are layout based on degree value.

It is pointed out that albumin is a cancer marker (Lv et al., 2018). It is reported that apo A1 and albumin play a crucial role in glioma tumor growth, migration, and angiogenesis (Hashemi et al., 2014). Based on this investigation, upregulation of apolipoprotein A1 and albumin occurs in astrocytoma brain tumors. Nieder et al suggested that the patients with brain metastasis who present dysregulated albumin levels in combination with elevated lactate dehydrogenase and also the occurrence of extracranial metastases to at least two organs should be considered for the finest kind of care (Nieder et al., 2014).

As shown in Figure 1, IL6 is the first neighbor of ALB, another common central node (hub-bottleneck) of migraine and gliosarcoma cancer networks. Comparing Figure 1 and Table 2 indicates that VEGFA, IL6, and FN1 are the first neighbors of ALB which are central nodes of the gliosarcoma cancer network. On the other hand, the comparison of Tables 1, 2 and Figure 2 show no common proteins between the first neighbors of IL6 and central nodes of migraine and gliosarcoma cancer networks.

Il6 is the second common hub bottleneck between migraine and gliosarcoma. It is reported that glioma stem cells, but not the bulk glioma cells, are responsible to initiate microglial IL-6 secretion. This process occurs via Toll-like receptor-4 signaling, which regulates secretion of IL-6 in glioma development (Dzaye et al., 2016). On the other hand, documents exist about the elevation of intracranial interleukin-6 in patients during migraine attacks. The involvement of IL6 and IL1β in the pathogenesis of migraine is investigated by D Han (Han, 2019; Yan et al., 2012).

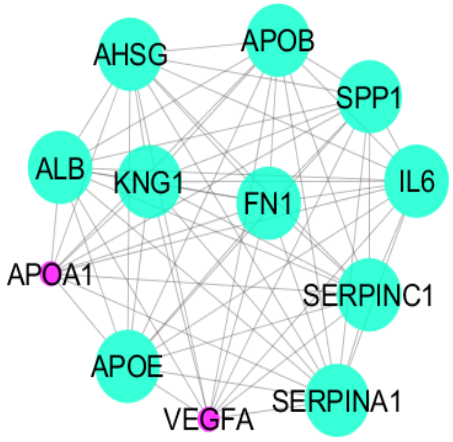

Figure 3. Albumin-interleukin 6 (ALB-IL6) and the 10 first neighbors from STRING database

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Nodes are layout based on degree value.

The first neighbors of ALB-IL6 paired nodes that are linked to the migraine and gliosarcoma networks are VEGFA, neurofibromatosis type I (NF1), and KNG1. KNG1 is a common protein between central nodes of the migraine network and the first neighbors of ALB-IL6 while VEGFA and NF1 like central nodes of the gliosarcoma cancer network to the first neighbors of ALB-IL6 paired proteins. The role of KNG1 in migraine is highlighted by Zamanian-Azodi et al. Based on this assessment, KNG1 inhibits nitric oxide synthase 3 (NOS3) which is a hub node in the protein-protein interaction network of migraine (Zamanian-Azodi et al., 2019). Zhang et al suggested VEGFA Fms-related receptor tyrosine kinase 1 (FLT1) and kinase insert domain receptor (KDR) messenger ribonucleic acid (mRNA) expression as prognostic factors in brain tumors (Zhang et al., 2015). NF1 is associated with abnormalities in the regulation of astrocytes and also the promotion of brain tumors. As reported by Dasgupta et al, neurofibromin is involved in the proliferation and survival of neural stem cells and also regulates astroglial differentiation (Dasgupta & Gutmann, 2005).

5. Conclusion

In conclusion, several molecular linkers are observed between migraine and brain cancers; however, ALB and IL6 can be considered two critical individuals. Also, network analysis revealed that several ALB-IL6 first neighbors are connected to the central elements of protein-protein interaction networks of migraine and gliosarcom.

Ethical Considerations

Compliance with ethical guidelines

This project is approved by Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1399.1203).

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Authors' contributions

Project is designed by Vahid Mansouri and all authors are participated equally in project administration and manuscript preparation.

Conflict of interest

The authors declared no conflict of interest.

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