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Title: Introducing Albumin and Interleukin 6 As Common Critical Dysregulated Proteins Between Migraine and Gliosarcoma

Running title: Introducing Common Central Proteins Between Migraine and Gliosarcoma

Authors: Mostafa Rezaei Tavirani^{1,*}, Vahid Mansouri¹, Babak Arjmand², Sina Rezaei Tavirani³

1. *Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
2. *Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.*
3. *Proteomics Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

***Corresponding author:** Mostafa Rezaei Tavirani, Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: tavirany@yahoo.com

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Abstract:

Introduction: It is reported that migraine may be risk factor of brain cancers. Since the one of the best ways to assess this possible relationship is molecular mechanism study, 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 STRING database and interacted via Cytoscape software to form two separate networks. Central nodes of the networks are compared to find the common central differentially expressed proteins. First neighbors of the common central proteins are studied.

Results: Numbers of 11 hub-bottlenecks for each one of migraine and gliosarcoma cancer networks were identified. Albumin and interleukin 6 as common differentially expressed central proteins were introduced. KNG1, VEGFA, and NF1 the first neighbors of ALB-IL6 were connected to the central nodes of networks of the two studied diseases.

Conclusion: Network analysis revealed that ALB and IL6 are common central dysregulate proteins between migraine and brain cancers. There are crucial proteins among the first neighbors of ALB and IL6 which are connected to migraine and gliosarcom.

Keywords: Migraine, Gliosarcoma, Albumin, Interleukin 6, Network analysis.

Introduction

Migraine is known as a public and sometimes devastating disorder [1]. It is reported that migraine is associated with several disorders such as cardiovascular diseases, gastrointestinal disorders, and vertigo [2, 3]. There are evidences about association between migraine and development of brain tumors [4]. Several studies are discussed molecular mechanism of Migraine and are pointed to the genes and proteins which are involved in migraine development [5, 6].

Protein-protein interaction network analysis is a suitable method to assess molecular mechanism of diseases. In this method set of proteins or genes which are involve in the evaluated disease connect to form an interactome. Since numbers of interaction and first neighbors of each protein may differ from others, role of elements of network is different from the other proteins. In scale free networks there are limited top nodes based on number of first neighbors or connections with the first neighbors. These nodes are known as hubs and play crucial role in the network construction [7, 8]. Based on shortest paths that are attributed to a node, bottleneck nodes are announced. Bottlenecks are known as central nodes of a network that have significant role in integration of network [9]. A hub node which acts as bottleneck is known as hub-bottleneck. The hub-bottleneck nodes are powerful elements of network and are considered as critical nodes [10].

Hub, bottleneck, and hub-bottleneck nodes are used to detect molecular mechanism of many diseases [11, 12].

Data sources in network analysis can be considered as databases or an experimental investigation. STRING is a known database that includes many diseases and related dysregulated proteins [13]. In the present study, the dysregulated proteins of migraine and gliosarcoma are extracted from STRING database and analyzed by network analysis to find central nodes that link migraine to gliosarcoma. ALB and IL6 are highlighted as critical linker between the two studied diseases.

Methods

Numbers of 200 related proteins for migraine were searched from “disease query” of STRING database. The extracted proteins were interacted via undirected edges by using Cytoscape software v3.7.2. The network was analyzed by “NetworkAnalyzer” application of Cytoscape software. The top 10% of nodes of the main connected component based on degree value and betweenness

centrality were selected as hubs and bottlenecks respectively. The common hubs and bottlenecks were identified as hub-bottlenecks.

As like migraine, 200 dysregulated proteins which were related to gliosarcoma were extracted from 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 “NetworkAnalyzer”. The hub-bottlenecks of the analyzed main component were introduced.

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 STRING database. Finally, resulted common hub-bottlenecks and the first neighbors were assessed and discussed.

Results

The retrieved proteins which were related to migraine were included in a protein-protein interaction network. The network including 14 isolated proteins, a subnetwork containing 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% of top nodes based on degree value (18 proteins) were identified as hubs and similarly 18 bottlenecks were determined. Among The introduced hubs and bottlenecks, 11 hub-bottleneck nodes were introduced. The hub-bottlenecks are listed in the table 1.

The main connected component of gliosarcoma network was constructed from 187 nodes and 3732 undirected connections. Numbers of 13 proteins were isolated. Among 19 hubs and also 19 bottlenecks, 11 common hub-bottlenecks were identified. List of hub-bottleneck nodes is presented in the table 2.

Comparison of tables 1 and 2 indicates that ALB and IL6 are the two-common hub-bottlenecks between migraine and gliosarcoma diseases. For better understanding of the role of ALB and IL6 in promotion of the two studied diseases, 10 first neighbors of ALB, IL6, and ALB-IL6 are presented in the figures 1-3. First neighbors of ALB are presented in the figure 1 and are visualized based on degree value. Numbers of 10 first neighbors of IL6 which are mostly cytokines are shown

in the figure 2. A network including ALB-IL6 and the 10 first neighbors of this paired proteins is exposed in the figure 3.

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

Row	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	IL6	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

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

Row	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

Figure 1. ALB and its 10 first neighbors from STRING database. Nodes are layout based on degree value.

Figure 2. IL6 and its 10 first neighbors from STRING database. Nodes are layout based on degree value.

Figure 3. ALB-IL6 and the 10 first neighbors from STRING database. Nodes are layout based on degree value.

Discussion

There are many common features between different diseases especially aspects of diseases molecular mechanism [14, 15]. Investigating common key proteins which are common between migraine and brain cancers is a way to understand migraine as risk factor for these types of cancers. In the present study ALB and IL6 were identified as two central common proteins which play critical roles in the protein-protein interaction networks of the two studied diseases.

LM Jacobsen et al investigated urinary albumin excretion as endothelial dysfunction marker in patients with migraine [16]. Based on this research there is no significant increase of 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 relative to the controls [17].

It is pointed that albumin is a cancer marker [18]. It is reported that apo A1 and albumin play crucial role in glioma tumor growth, migration and angiogenesis [19]. Based on this investigation, upregulation of apolipoprotein A1 and albumin occurs in astrocytoma brain tumors. C Nieder et al suggested that the patients with brain metastasis which present dysregulated albumin level in combination with elevated lactate dehydrogenase and also occurrence of extracranial metastases to at least two organs should be considered for finest kind of cares [20].

As it is depicted in the figure 1, IL6 is a first neighbor of ALB, this protein is the other common central node (hub-bottleneck) of migraine and gliosarcoma cancer networks. Comparison of figure 1 and table 2 indicates that VEGFA, IL6, and FN1 are the first neighbors of ALB which are central nodes of gliosarcoma cancer network. In the other hand comparison of tables 1-2 and figure 2 shows that there are no common proteins between the first neighbors of IL6 and central nodes of migraine and gliosarcoma cancers 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 secretion of IL-6 regulates glioma development [21]. In the other hand there are documents about elevation of intracranial interleukin-6 in patients during migraine attacks. Involvement of IL6 and IL1 β in pathogenesis of migraine is investigated by D Han [22, 23].

The first neighbors of ALB-IL6 paired nodes which are linked to the migraine and gliosarcoma networks are VEGFA, NF1, and KNG1. KNG1 is a common protein between central nodes of migraine network and the first neighbors of ALB-IL6 while VEGFA and NF1 like central nodes of gliosarcoma cancer network to first neighbors of ALB-IL6 paired proteins. Role of KNG1 in migraine is highlighted by Zamanian-Azodi et al. based on this assessment, KNG1 inhibits NOS3 which is a hub node in the protein-protein interaction network of migraine [24]. SD Zhang et al suggested VEGFA FLT1 and KDR mRNA expression as prognostic factors in brain tumors [25]. Neurofibromatosis 1 (NF1) is tied to abnormalities in regulation of astrocyte and also promotion of brain tumors. As it is reported by Dasgupta et al, neurofibromin play roles in proliferation, survival of neural stem cell and also regulates astroglial differentiation [26].

Conclusion

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

Conflict of interest

There is no conflict of interest.

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