ORIGINAL ARTICLE

Identify Candidate Genes in the Interaction between Abdominal Aortic Aneurysm and Type 2 Diabetes Mellitus by Using Biomedical Discovery Support System

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Key words: abdominal aortic aneurysm; diabetes mellitus; Biomedical Discovery Support System; text mining; gene expression profile

Objective To explore the candidate genes that play significant roles in the interconnection between abdominal aortic aneurysm (AAA) and type 2 diabetes mellitus (DM).

Methods We used the Biomedical Discovery Support System (BITOLA) to screen out the candidate intermediate molecular (CIM) "Gene or Gene Product" that are related to AAA and DM. The dataset of GSE13760, GSE7084, GSE57691, GSE47472 were used to analyze the differentially expressed genes (DEGs) of AAA and DM compared to the healthy status. We used the online tool of Venny 2.1 assisted by manual checking to identify the overlapped DEGs with the CIMs. The Human eFP Browser was applied to examine the tissue specific expression levels of the detected genes in order to recognize strong expressed genes in both human artery and pancreatic tissue.

Results There were 86 CIMs suggested by the closed BITOLA system. Among all the DEGs of AAA and DM, 8 genes in GSE7084 (ISG20, ITGAX, DSTN, CCL5, CCR5, AGTR1, CD19, CD44) and 2 genes in GSE13760 (PSMD12, FAS) were found to be overlapped with the 86 CIMs. By manual checking and comparing with tissue-specific gene data through Human eFP Browser, the gene PSMD12 (proteasome 26S subunit, non-ATPase 12) was recognized to be strongly expressed in both the aorta and pancreatic tissue.

Conclusion We proposed a hypothesis through text mining that PSMD12 might be involved or potentially involved in the interconnection between AAA and DM, which may provide a new clue for studies on novel therapeutic strategies for the two diseases.

ABDOMINAL Aortic Aneurysms (AAA) is defined by an abdominal aortic dilation of 3 cm or more, commonly due to atherosclerosis.^[1] Ultrasound screening and autopsy

studies have shown that the prevalence of AAA is 4% - 8% in men and 1% - 1.3% in women in population of over 50 years old, and 12.5% in men and 5.2% in women in elderly people of 74 - 84 years old.^[2, 3] AAA patients have a high mortality rate up to 90% due to AAA rupture.^[3] The main risk factors include aging, being male, smoking, hyperlipidemia, inflammation, family history of AAA, and hypertension.^[4, 5]

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Diabetes Mellitus (DM) is a common disease which affects more than 415 million people in the world and 92.4 million people in China, as reported in 2015.^[6, 7] In patients with poor glycemic control, this disease could lead to micro- or macroangiopathy which is always the basic pathology of blindness, renal disease, amputations, etc.^[8-10] In spite of the systemic atherosclerosis commonly observed in diabetes, the prevalence of AAA is relatively low in diabetic patients.^[11-13] The reason for the negative correlation between AAA and DM, and the underlying mechanism are unclear. Therefore, the potential interaction should be further investigated.

With the continuous advance of biomedical science, scientists can obtain a large amount of information by searching literature using specific keywords, but the essence of the literature still needs manual review, which makes it difficult to explore all relevant information in a short period of time.^[14, 15] With invention of computer-supported literature mining tools, scientists can infer implicit knowledge from literature databases and propose testable hypotheses. This process, named as literature-based discovery (LBD),^[16, 17] was first carried out by Don Swanson, who found that fish oil may be beneficial to patients with Raynaud's disease.^[18]

Using the Swanson's ABC model, investigators search the indirect relations and propose hypothesis in two unrelated diseases.^[19] The model is usually implemented in two main methods: one is the open discovery process, which is characterized by origination of a hypothesis; the other is the closed discovery process, which is characterized by the elaboration of a hypothesis.^[20, 21] All the specific work requires text mining tools to carry them out. There is a summarization of text mining tools in Weeber's review.^[21] Based on these tools, researchers have identified multiple latent genes or potential drug mechanisms for diseases.^[16, 22-24]

In this study, we applied text mining tools to explore potential genes that may be involved in the interconnection between AAA and DM, which might be the first attempt on this topic.

MATERIALS AND METHODS

Searching the intermediate concepts

Biomedical Discovery Support System (BITOLA) is based on interactive literature. We used the closed discovery process of BITOLA to find new relationships

between AAA and DM. The medical subject headings (MeSH) and human genes from the Human Genome Organization (HUGO) were regarded as "A" and "C", respectively in the BITOLA system.^[26] We retrieved two pieces of corresponding documents from two starting fields "A" and "C"; meanwhile, the common term "B" appears in both pieces of the documents; accordingly, we chose "B" as the potential hypothesis.^[24] The algorithm of the closed discovery process we used to explore medical concepts with BITOLA is shown in **Fig. 1.**^[21]

Tentatively, "Aortic Aneurysm, Abdominal" was utilized as the beginning concept (Unified Medical Language System, semantic types: disease or syndrome), and "Diabetes Mellitus, Non-Insulin-Dependent" was regarded as the terminal concept (disease or syndrome). As a result, we obtained the candidate intermediate concept (CIM) through the retrieval of the closed system.

We tentatively filtered and assessed the intermediate concepts of "Gene or Gene product" through review "Gene or Gene Product" mRNA expression level under disease conditions or control conditions.

Gene expression profiles

As many reasons can lead to different gene expression profiles, in this study, we focused on detecting "genes or gene product" that are differentially expressed in disease and healthy status, i.e., AAA vs. control, and DM vs. control. The differentially expressed gene (DEGs) was reserved for further analysis; otherwise, it was excluded.

Gene expression data sets were acquired from

Figure 1. Closed discovery process in the BITOLA system. The search process starts simultaneously from AAA and DM, resulting in overlapping G_n . The dashed arrows indicate potentially interesting "gene or gene product" of discovery; the solid arrows indicate unsuccessful "gene or gene product". AAA, abdominal aortic aneurysm; DM, diabetes mellitus.

the gene expression omnibus (GEO) database.^[25] The network tool GEO2R was used to analyze the differentially expressed genes between the disease states and the normal controls.^[26] The top 250 probes were changed into gene names and designated for further analysis. T-test was used to sort out the DEGs.

As this research mainly focused on the artery tissue, for DM, we used GSE13760 which was developed from arterial intima media of 10 patients with type 2 diabetics and 11 normal controls;^[27] for AAA, dataset of GSE7084, GSE57691, GSE47472 were used for analysis.^[28-30]

Filtering intermediate concepts by manually checking and tissue-specific gene expression visualizing

Online visual analysis tool Venny 2.1 (<https://bioinformatics.csic.es/tools/venny/>) was used for CIM and DEGs intersection analysis. To avoid false-positives in text mining, we looked over the “gene or gene product” by reading the original literature to exclude the ambiguous term. The remaining “genes or gene products” were further examined for tissue-specific expression using Human Electronic Fluorescent Pictograph Browser (http://www.bar.utoronto.ca/efp_human/cgi-bin/efpWeb.cgi) with data sources of “circulatory-respiratory” and “skeletal-immune-digestive” in “absolute” mode to visualize expressions of the screened out genes in extensive human gene expression datasets of human body and to identify the highly expressed “Gene or Gene Product” in arterial tissue and pancreatic tissue.^[31]

RESULTS

Intermediate conception

The search of the intermediate concept with respect to “Gene or Gene Product” from the beginning concept to end concept yielded 86 CIMs (Supplementary **Table S1**), as suggested by the closed BITOLA system.

Differentially expressed genes

Among all the DEGs recognized through analysis of datasets GSE13760, GSE7084, GSE57691, GSE47472 (Supplementary **Table S2**), eight genes in GSE7084 (ISG20, ITGAX, DSTN, CCL5, CCR5, AGTR1, CD19, CD44) and two genes in GSE13760 (PSMD12, FAS) were identified to be overlapped with the 86 CIMs (**Table 1**).

Manual checking result

Among the DEGs recognized above, the gene DSTN was excluded because the abbreviations or alternative name used in an article referred to “aortoduodenal fistula (ADF)” instead of the original concept of “gene or gene product” by DSTN.

Tissue specific gene expression in artery and pancreatic tissue

The gene expression levels of the remaining genes (ISG20, ITGAX, CCL5, CCR5, AGTR1, CD19, CD44, PSMD12, FAS) in arterial tissue and pancreatic tissue were examined through the human eFP browser. PSMD12 was identified as the most remarkable gene with strong expression in both aorta and pancreatic tissue (**Fig. 2**). The expressions of the other detected genes were all very low in the two tissues.

DISCUSSION

AAA is a vascular atherosclerotic disease with complex pathologic processes that involve oxidative stress, inflammation, and proteolytic pathways.^[4, 5, 26] DM have many complications, which share the same pathological basis—atherosclerosis.^[31] Interestingly, researchers have found that patients with diabetes have a low incidence of AAA despite the fact that AAA is one of the clinical manifestations of atherosclerotic diseases.^[12, 32, 33] The underlying mechanisms are still unknown. The integration of LBD and gene expression data in this

Table 1. Differentially expressed genes of the abdominal aortic aneurysm and diabetes mellitus based on microarray platforms.

Disease	Series	Tissue	Subjects		Array platform	Overlap with CIM
			Control	study		
Abdominal Aortic Aneurysm	GSE7084	Human abdominal aorta	2	2	Affymetrix	ISG20, ITGAX, DSTN, CCL5, CCR5, AGTR1, CD19, CD44
	GSE57691	Human abdominal aorta	10	49	Illumina	None
	GSE47472	Full thickness aorta biopsy	8	14	Illumina	None
Diabetes Mellitus	GSE13760	Arterial intima-media	11	10	Affymetrix	PSMD12, FAS

CIM, candidate intermediate molecules. GSE, Government Sponsored Enterprise.

Figure 2. Human Electronic Fluorescent Pictograph browser output showing high expressions of PSMD12 in both aorta and pancreatic tissues. (A) "Anatogram" and (C) histogram of PSMD12 expressions by the data source of "circulatory-respiratory" system. (B) "Anatogram" and (D) histogram of PSMD12 expressions by the data source of "skeletal-immune-digestive" system.

study may provide insight into the molecular mechanisms in the interconnection between AAA and DM.

The discoveries of LBD need following verification in laboratories or in clinics.^[20, 23, 24] Researchers have used LBD in a variety field to explore the possible mechanisms between two related diseases.^[22, 34] In this study, "Aortic Aneurysm, Abdominal" was used as the starting concept and "Diabetes Mellitus" as the end concept. We found 10 genes (ISG20, ITGAX, DSTN, CCL5, CCR5, AGTR1, CD19, CD44, PSMD12, FAS) as the possible intermediates. DSTN was removed by the follow-up filter because DSTN in the text was for "aortoduodenal fistula (ADF)".^[25] The remaining genes were found to express extremely low by Human eFP Browser except for PSMD12, which was proposed as the potential related gene.

PSMD12 (proteasome 26S subunit, non-ATPase 12), also called Rpn5, is localized on chromosome 17q24.2 and has 13 exons. The product of this gene is a non-ATPase, subunit of the 19S regulator. The 19S regulator is one of the two main compositions of the 26S proteasome which belongs to the ubiquitin-proteasome system (UPS).^[35] Research found that the inducible knockdown of RPN5 had a vital inhibitory effect on Toll and IMD-mediated NF- κ B activation, so Rpn5 might be a mechanosensitive NF- κ B activator.^[36] Study also reveal that the expression of osteopontin and NF- κ B elevate in human aortic aneurysms, which accelerate the degradation of the extracellular matrix and play a significant role in pathogenesis and development of thoracic aortic aneurysm and AAA.^[37] In addition, intracellular NF- κ B signaling plays an important role in remodeling of blood vessels and formation of aneurysms.^[38] Meanwhile, it was found that the NF- κ B pathway was involved in regulating macrovascular pathology and vascular smooth muscle cells phenotype in type 2 diabetes.^[39] Furthermore, Yen HC *et al.* suggested that Rpn5 may play a unique role in regulating assembly of the proteasome, which can also be mismatched in cells lacking Rpn5.^[40] The proteasome is the degradation arm of the ubiquitin system, mainly involved in protein degradation, thereby regulate cell cycle, cell growth and differentiation, signal transduction, and other biological processes.^[41] Subsequently, a disordered proteasome assembly and function contribute to the pathogenesis and phenotypic characteristics in cardiovascular diseases,^[42] diabetes mellitus,^[43] inflammatory responses,^[44] and so on. The PSMD12 may be the molecular connection between AAA and DM by

affecting the NF- κ B pathway or the assembly of proteasome. The function of PSMD12 in the interaction of AAA and DM needs further investigations.

The main deficiencies of this study is that although the bioinformatics and text mining method can find out potential new conceptual connections, there has no objective system or gold standard for evaluation in the field of text mining. The results may be biased, therefore always need further experimental and clinical verification. In conclusion, the current study investigates the interaction of AAA and DM using text mining tools, and proposes that PSMD12 may be involved in the interconnection between AAA and DM. This result may provide a new clue for studies on innovative treatment strategies for the two diseases in future.

Supplementary materials

Table S1 and Table S2 are available online at <http://cmsj.cams.cn/EN/10.24920/003711>.

Conflict of interests

None.

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应用 BITOLA 系统筛选腹主动脉瘤 与 2 型糖尿病相互作用的候选基因

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摘要

目的 应用生物信息学方法识别并挖掘腹主动脉瘤和糖尿病相互作用的候选基因。

方法 采用封闭的生物医学发现支持系统 (Biomedical Discovery Support System, BITOLA), 筛选与腹主动脉瘤和糖尿病有关的“基因或基因产物”作为候选中间分子 (candidate intermediate molecules, CIMs)。通过 GSE13760, GSE7084, GSE57691, GSE47472 数据集筛选分别与腹主动脉瘤和糖尿病发病相关的差异表达基因 (differentially expressed genes, DEGs)。然后, 我们通过 Venny2.1 在线工具, 辅以人工阅读文献, 筛选出与 CIMs 重合的差异性表达基因。最后, 应用基因表达人体电子荧光可视化浏览器 (Human eFP Browser) 观测所筛选出的基因的组织特异性表达, 确定在动脉和胰腺组织均高表达的候选基因。

结果 应用封闭的生物医学发现支持系统筛选出 86 个 CIMs。在 GSE13760, GSE7084, GSE57691, GSE47472 数据集与腹主动脉瘤和糖尿病相关的差异表达基因中, 我们发现 GSE7084 数据集中的 8 个基因 (ISG20, ITGAX, DSTN, CCL5, CCR5, AGTR1, CD19, CD44) 和 GSE13760 数据集中的 2 个基因 (PSMD12, FAS) 与 86 个 CIMs 交叉重叠。通过电子荧光可视化人体基因表达象形图进行组织特异性验证发现, 基因 PSMD12 在主动脉和胰腺组织中均有高表达。

结论 通过生物信息文本挖掘技术我们提出假说, PSMD12 可能参与腹主动脉瘤与糖尿病的相互作用, 这可能成为研究这两种疾病新型治疗手段的新线索。

关键词: 腹主动脉瘤; 2 型糖尿病; 生物医学发现支持系统; 文本挖掘; 基因表达谱