Interrelationship Between 2019-nCov Receptor DPP4 and Diabetes Mellitus Targets Based on Protein Interaction Network

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Abstract

Objective: Exploring the relationship between diabetes mellitus targets and DPP4 of the receptor of novel coronavirus (2019-nCoV) through a protein interaction network to provide new perspective for clinical medication.

Methods: Diabetes mellitus targets were obtained from GeneCards database. Targets with a relevance score exceeding 20 were included, and DPP4 protein was added manually. The initial protein interaction network was obtained through String. The targets directly related to DPP4 were selected as the final analysis targets. Importing them into String again to obtain the protein interaction network. Module identification, GO analysis and KEGG pathway analysis were carried out respectively. The impact of DPP4 on the whole network was analyzed by scoring the module where it located.

Results: 43 DPP4-related proteins were finally selected from the diabetes mellitus targets and three functional modules were found by the cluster analysis. Module 1 was involved in insulin secretion and glucagon signaling pathway, module 2 and module 3 were involved in signaling receptor binding. The scoring results showed that LEP and apoB in module 1 were the highest, and the scores of INS, IL6 and ALB of cross module associated proteins of module 1 were the highest.

Conclusions: DPP4 is widely associated with key proteins in diabetes mellitus. COVID-19 may affect DPP4 in patients with diabetes mellitus, leading to high mortality of diabetes mellitus combined with COVID-19. DPP4 inhibitors and IL-6 antagonists can be considered to reduce the effect of COVID-19 infection on diabetic patients.

1. Introduction

Due to the high prevalence and long incubation periods often without symptoms, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected hundreds of millions of people around the world, causing the coronavirus disease 2019 (COVID-19) pandemic.[1]. Recent studies have shown that DPP-4 is one of the functional receptors of human coronavirus.[2–5] SARS-CoV-2 Virus S protein can infect the body by acting on this receptor of bronchiolar epithelial cells.[6] Dipeptidyl peptidase-4(DPP4) also known as CD26, is a serine exopeptidase, a multifunctional type-II transmembrane glycoprotein that presents in a dimeric form on the cell surface. DPP4 is multifunctional, highly conserved among mammals. It regulate the activities of peptide hormones, neuropeptides, cytokines and growth factors, but also act as a surface antigen to cooperate with other molecules or proteins to mediate the interaction between cells and matrix, cells and cells, and play various regulatory roles in immune activation, inflammatory response and tumorigenesis.[7]

DPP4 inhibitors are a kind of hypoglycemic drugs which have been widely used. DPP4 can decompose glucagon like peptide-1 (GLP-1), which can stimulate insulin secretion and DPP4 inhibitors can effectively antagonize this effect. They can control blood glucose, especially postprandial blood glucose, and

improve glucose tolerance, insulin resistance and other symptoms of patients by inhibiting the degradation of GLP-1.[8] Diabetic patients are more likely to be infected with COVID-19, and the risk of death is significantly higher than ordinary patients. [9–10] Current studies have shown that DPP4 inhibitors can be considered as the preferred hypoglycemic regimen in the treatment of diabetic patients with COVID-19 infection.[11] In order to strengthen the management of diabetic patients with COVID-19, we intend to study the protein interaction through the protein interaction network, and evaluate the degree of protein-protein correlation through the correlation score. Based on the String database, this paper analyzes the relationship between DPP4 and diabetic protein targets, in order to find a new clue for the management of diabetic patients with COVID-19.

2. Materials And Methods

2.1. Get diabetes mellitus targets information

All targets of diabetes mellitus were obtained through GeneCards database (https://www.genecards.org/). Targets with a relevance score exceeding 20 were included, and DPP4 protein was added manually as target point.

2.2. Screening of protein targets directly associated with DPP4

The target was imported into the STRING (https://string-db.org/) [12] in the form of symbol to obtain the initial protein network, and the targets directly related to DPP4 was screened.

2.3. Construction of DPP4 related protein network

DPP4 and 43 related proteins were re-imported into STRING to obtain the protein interaction network for subsequent analysis.

2.4. Identification and analysis of DPP4 related protein network modules

K-means algorithm was used to cluster the above protein interaction networks.

2.5. Gene ontology(GO)and Kyoto encyclopedia of genes and genomes（KEGG）pathway analysis of each module

GO analysis and KEGG pathway analysis of all modules are further carried out through STRING.

2.6. Evaluation of the impact of DPP4 on the whole protein network

In order to further evaluate the impact of DPP4 on the whole network and the possible pathway, the module 1 where DPP4 is located is used as the internal network, the cross module association of internal network is screened out. The statistical description and mapping are carried out. The data are filtered with 0.6 (determined by mean and median) as the standard, the qualified cross module associated proteins and associated scores were listed, and the proteins included in module 1 and the cross module associated protein scores of module 1 were summed as the scores.

3. Results

3.1. Screening results of DPP4 associated proteins

A total of 1031 diabetes mellitus targets and 43 targets directly related to DPP4 were obtained by screening (Table 1).

Table 1
DPP4 related protein

Symbol	Protein Name	Score
ACE	Angiotensin-converting enzyme	0.709
ADIPOQ	Adiponectin	0.572
AKT1	RAC-alpha serine/threonine-protein kinase	0.52
ALB	Serum albumin	0.671
APOB	Apolipoprotein B-100	0.438
APOE	Apolipoprotein E	0.422
CAV1	Caveolin-2	0.692
CCL2	C-C motif chemokine 2	0.448
CCR5	C-C chemokine receptor type 5	0.4
CPE	Carboxypeptidase E	0.438
CRP	C-reactive protein	0.536
CTLA4	Cytotoxic T-lymphocyte protein 4	0.44
CXCL10	C-X-C motif chemokine 10	0.581
FN1	Fibronectin type III domain containing	0.773
GCG	Glucagon	0.994
GCGR	Glucagon receptor	0.573
GCK	Glucokinase	0.461
GGT1	Glutathione hydrolase 1 proenzyme	0.411
GHRL	Appetite-regulating hormone	0.559
GLP1R	Glucagon-like peptide 1 receptor	0.899
GPT	Alanine aminotransferase 1	0.508
HNF1A	Hepatocyte nuclear factor 1-alpha	0.538
IAPP	Islet amyloid polypeptide	0.672
ICAM1	Intercellular adhesion molecule 1	0.441
IL10	Interleukin-10	0.41
IL6	Interleukin-6	0.514
INS	Insulin	0.942

Symbol	Protein Name	Score
INS-IGF2	Insulin, isoform 2	0.535
LEP	Leptin	0.593
MMP2	72 kDa type IV collagenase	0.404
MMP9	Matrix metalloproteinase-9	0.405
NOS3	Nitric oxide synthase, endothelial	0.658
NPY	Pro-neuropeptide Y	0.735
PPARG	Peroxisome proliferator-activated receptor gamma	0.51
REN	Renin	0.499
SERPINE1	Plasminogen activator inhibitor 1	0.454
SLC2A2	Solute carrier family 2, facilitated glucose transporter member 2	0.462
SLC2A4	Solute carrier family 2, facilitated glucose transporter member 4	0.461
SLC5A2	Sodium/glucose cotransporter 2	0.892
SST	Somatostatin	0.472
TNF	Tumor necrosis factor	0.473
VCAM1	Vascular cell adhesion protein 1	0.416
VEGFA	Vascular endothelial growth factor A	0.643

3.2. Protein interaction network results

The network consists of 44 nodes and 570 edges. The average value of nodes is 25.9. (Fig. 1).

3.3. Cluster analysis results of protein interaction network

Three functional modules were obtained by cluster analysis. Module 1 includes 17 nodes (SLC5A2、SLC2A2、LEP、GCG、DPP4、ADIPOQ、APOB、GGT1、GPT、NPY、GCK、CPE、SST、GCGR、IAPP、GLP1R、GHRL); module 2 includes 14 nodes (ICAM1、VCAM1、APOE、CCL2、TNF、CRP、IL6、ALB、ACE、HNF1A、CCR5、CXCL10、IL10、PPAARG); module 3 includes 13 nodes Nodes (MMP2、MMP9、FN1、VEGFA、 CAV1、CTLA4、NOS3、AKT1、INS、SLC2A4、REN、SERPINE1、INS-IGF2) (Fig. 2).

3.4. GO analysis and KEGG analysis

Through GO analysis and KEGG analysis, it was found that the target of module 1 was mainly enriched in insulin secretion and glucagon signal transduction pathway; the target of module 2 and module 3 was mainly enriched in signaling receptor binding.

3.5. Module 1 cross module correlation statistics results

Module 1 contains 190 cross module associations, accounting for 33% of the total number of network associations (570). The average score of association is 0.649, and the median is 0.628 (Table 2).

Table 2
GO and KEGG analysis of different modules

Module	Protein	GO and KEGG analysis	*P*
Module 1	SLC5A2、SLC2A2、LEP、GCG、DPP4、ADIPOQ、APOB、GGT1、GPT、NPY、GCK、CPE、SST、GCGR、IAPP、GLP1R、GHRL	GO: hormone activity KEGG: Maturity onset diabetes of the young; Insulin secretion; Glucagon signaling pathway	1.29e-07 3.55e-05 3.55e-05 3.55e-05
Module 2	ICAM1、VCAM1、APOE、CCL2、TNF、CRP、IL6、ALB、ACE、HNF1A、CCR5、CXCL10、IL10、CCL2、PPAARG	GO: signaling receptor binding KEGG: African trypanosomiasis; TNF signaling pathway	2.63e-05 9.61e-08 9.61e-08
Module 3	MMP2、MMP9、FN1、VEGFA、 CAV1、CTLA4、NOS3、AKT1、INS、SLC2A4、REN、SERPINE1、INS-IGF2	GO: signaling receptor binding KEGG: Fluid shear stress and atherosclerosis	0.0030 2.14e-08

3.6. Module 1 cross module correlation impact assessment results

In module 1, LEP and apoB have the highest scores, which indicates that the above proteins may have cross module effects. The scores of INS, IL6 and ALB of cross module associated proteins of module 1 were the highest, which indicates that the effects of module 1 on other modules are more likely to be achieved through interaction with the above proteins (Table 3).

Table 3
Module 1 cross module associated protein and relevance score

APOB		**GGT1**		**GPT**		**NPY**		**CPE**	
NOS3	0.707	IL6	0.616	IL10	0.66	IL6	0.709	INS	0.97
VCAM1	0.74	CRP	0.669	TNF	0.707	INS	0.889		
IL10	0.751	INS	0.67	IL6	0.733	CXCL10	0.908		
MMP9	0.789	ALB	0.805	INS	0.839	CCR5	0.919		
TNF	0.793			CRP	0.896				
INS	0.848			ALB	0.924				
IL6	0.969								
SST		**GCGR**		**GHRL**		**GCG**		**LEP**	
ALB	0.621	INS	0.694	INS-IGF2	0.607	INS-IGF2	0.668	REN	0.662
AKT1	0.68			NOS3	0.628	SERPINE1	0.672	CAV1	0.682
CXCL10	0.908			IL6	0.63	ALB	0.704	INS-IGF2	0.7
INS	0.915			ALB	0.675	AKT1	0.776	MMP9	0.707
CCR5	0.922			AKT1	0.71	SLC2A4	0.793	VCAM1	0.722
				INS	0.944	INS	0.986	MMP2	0.724
								CCL2	0.732
								ICAM1	0.762
								NOS3	0.762
								APOE	0.775
								IL10	0.797
								ALB	0.803
								AKT1	0.841
								SLC2A4	0.856
								VEGFA	0.867
								SERPINE1	0.879
								TNF	0.9
								IL6	0.943
								INS	0.976

APOB	GGT1	GPT	NPY	CPE	
				CRP	0.981

4. Discussion

By sorting the correlation scores of DPP4 related proteins, we found that GCG, INS and GLP1R had the highest correlation scores, which were more than 0.8, and GCG and INS were more than 0.9, which meant that DPP4 was most closely related to the above diabetes related proteins. By cluster analysis, three functional modules were found. Module 1 was mainly involved in insulin secretion and glucagon signal transduction pathway including DPP4, while module 2 and module 3 were involved in signaling receptor binding. The binding of S protein of COVID-19 with DPP4 is the starting point of the course of the disease. In order to evaluate the possible influence and pathway of the virus after entering the human body, DPP4 is taken as the starting point of the whole network for in-depth analysis. Because there are a lot of low values in the correlation scores of DPP4 cross module associated proteins, the mean and median are used as the standard to filter the data, and the sum of the correlation scores is used as the score. It was found that LEP and apoB were the highest in module 1. The scores of INS, IL6 and ALB of cross module associated proteins of module 1 were the highest. It is worth noting that DPP4 cross module correlation scores are less than 0.6, so it does not shown. Therefore, the abnormal changes of DPP4 may not play an effect by directly interacting with module associated proteins, but may be that module 1 magnifies its effect, and this effect is transmitted to module 2 and module 3 through the close relationship between module 1 and INS, IL6 and ALB, resulting in the disorder of glucose metabolism and inflammatory regulation.

The data of clinical trials related to COVID-19 show that diabetic patients are more likely to be infected with SAR-COV-2, while the prognosis of patients with diabetes mellitus is worse and the risk of death is higher.[9–10] So, what is the mechanism of susceptibility to SAR-COV-2 in diabetic patients? What is the mechanism of higher risk of death and worse prognosis in patients with diabetes mellitus? How to guide the medication of diabetic patients infected with SAR-COV-2 in clinic? DPP4 as a type II transmembrane protein is also known to be cleaved from the cell membrane involving different metalloproteases in a cell-type-specific manner. Circulating, soluble DPP4 has been identified as a new adipokine, which exerts both para- and endocrine effects.[13] Recently, studies have found that sCD26 serum protein levels are reduced in diabetes. High serum sCD26 level could protect from viral infection by blocking the receptor from virus entry, whereas low sCD26 level may be associated with a higher risk of infection which may be one of the mechanisms of susceptibility to SARS-COV-2 in diabetic patients.[14] The high mortality of patients with COVID-19 are closely related to the disorder of glucose metabolism and inflammation regulation. [15] The S protein of SARS-COV-2 can invade T, NK and other immune cells through binding receptor DPP4, and activate nuclear factor - κ B (NF - κ b) pathway, resulting in the secretion of a series of pro-inflammatory cytokines, including interleukin-6 (IL-6). [16] IL-6 can promote the differentiation of T helper cell 17 (Th17) and other lymphocyte changes. Circulating IL-6 and soluble IL-6 receptor complexes indirectly activate

many types of cells, including endothelial cells, leading to the proliferation of a series of cytokines, leading to decreased blood pressure and acute respiratory distress syndrome (ARDS).[17] IL-6 plays a key role in this cascade. It suggests that people should evaluate the possibility of IL-6 antagonists (such as tocilizumab, sarilumab and siluximab) in the treatment of severe COVID-19 disease. DPP4 also degrades GLP-1 and GIP and plays an important role in glucose metabolism. Studies have shown that GLP-1-based therapy can reduce the activation of immune cells, inhibit the release of pro-inflammatory cytokines, and reduce organ dysfunction and mortality. [18] DPP4 inhibitor can increase the half-life of GLP-1 and play an indirect role. DPP4 inhibitors can also resist lung inflammation and reduce lung injury. [19] These studies suggest that DPP4 inhibitors may play an active role in the treatment of diabetic patients with COVID-19. However, the issue remains controversial. Males believes that DPP4 inhibitors inhibit the immune system and may increase the risk of infection. [20] However,There are also studies that show that the use of DPP4 inhibitors does not have a negative impact. [21] Previous retrospective studies have found that DPP4 inhibitors have serious heterogeneity in the treatment effect of COVID-19. [22–28] However, these studies are not randomized controlled double-blind studies. At present, three randomized controlled trials (NCT 04341935、NCT 04371978、NCT04365517)(Retrieved from: https://clinicaltrials.gov/) are ongoing to study the effect of DPP4 inhibitors on the prognosis of COVID-19 and the clinical results are expected to be obtained as soon as possible.

Leptin was the protein with the highest cross module effect in module 1, with a score of 16.071. Leptin is a hormone secreted by adipose tissue. When the body fat is reduced or in a low-energy state (such as starvation), leptin will decrease significantly, thus stimulating the food seeking behavior and reducing its own energy consumption. On the contrary, when the body fat increases, leptin increases, which inhibits eating and accelerates metabolism. [29] Leptin not only regulates body weight, but also is associated with monocyte activation and severe illness in patients with COVID-19.[30] Overweight patients with COVID-19 tend to have higher leptin levels, which further activates monocytes, leading to amplification or imbalance of immune response, which may also be the mechanism of overweight patients more prone to serious diseases. [31] CRS is one of the important causes of death in patients with COVID − 19. However, the changes of cytokine profile and the underlying mechanism are still unknown. Using the cytokine array containing 174 cytokines related to inflammation found that the cytokine spectrum of severe patients with COVID-19 was significantly different from that of mild patients or healthy controls. Leptin, CXCL-10, IL-6, IL-10, IL-12, TNF and other cytokines, indicating that these inflammatory factors can predict the severity of COVID − 19 disease.[32] The cluster analysis showed that leptin in module 1 and IL-6, IL-10, TNF in module 2 had a cross model effect, and the highest score of IL-6 was 6.163, which further suggested the possibility of IL-6 antagonists in the treatment of severe COVID-19 disease.

In this paper, we screened out the diabetes related proteins and functional modules closely related to DPP4 through protein interaction network, and analyzed the influence of DPP4 module 1 on the whole protein network and the possible pathway. It was proposed that the influence of COVID-19 infection was amplified by DPP4 in diabetic patients, and through its interaction with INS, leptin, IL-6 and other proteins. Increased glucose metabolism disorder and excessive inflammatory reaction lead to the high mortality in

diabetic patients with COVID-19. At present, the data of retrospective observational studies show that the therapeutic effect of DPP4 inhibitors has serious heterogeneity, but the strength of the above studies is low. We look forward to further randomized controlled trials to verify our inference.

5. Conclusions

DPP4 is widely associated with key proteins in diabetes mellitus. COVID-19 may affect DPP4 in patients with diabetes mellitus, leading to high mortality of diabetes mellitus combined with COVID-19. DPP4 inhibitors and IL-6 antagonists can be considered to reduce the effect of COVID-19 infection on diabetic patients.

Abbreviations

DPP4 = Dipeptidyl peptidase-4；COVID-19 = coronavirus disease 2019；GO = gene ontology；KEGG = Kyoto encyclopedia of genes and genomes；GLP-1 = glucagon like peptide-1

Declarations

Author contributions

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Formal analysis：Tingting Li.

Writing：Qian Gao.

All authors read and approved the final manuscript.

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Figures

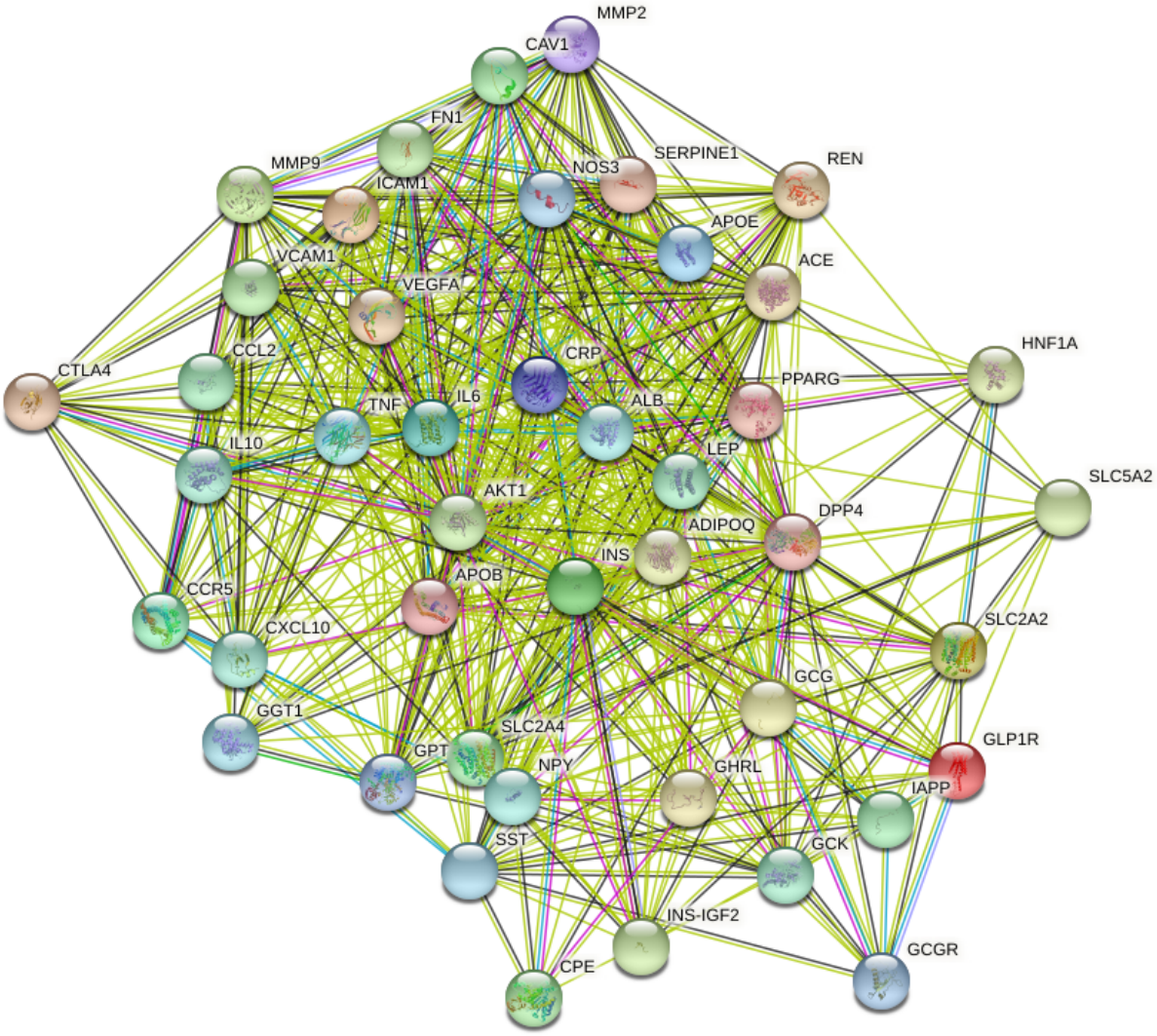

Figure 1

Interaction networ of DPP4 related protein

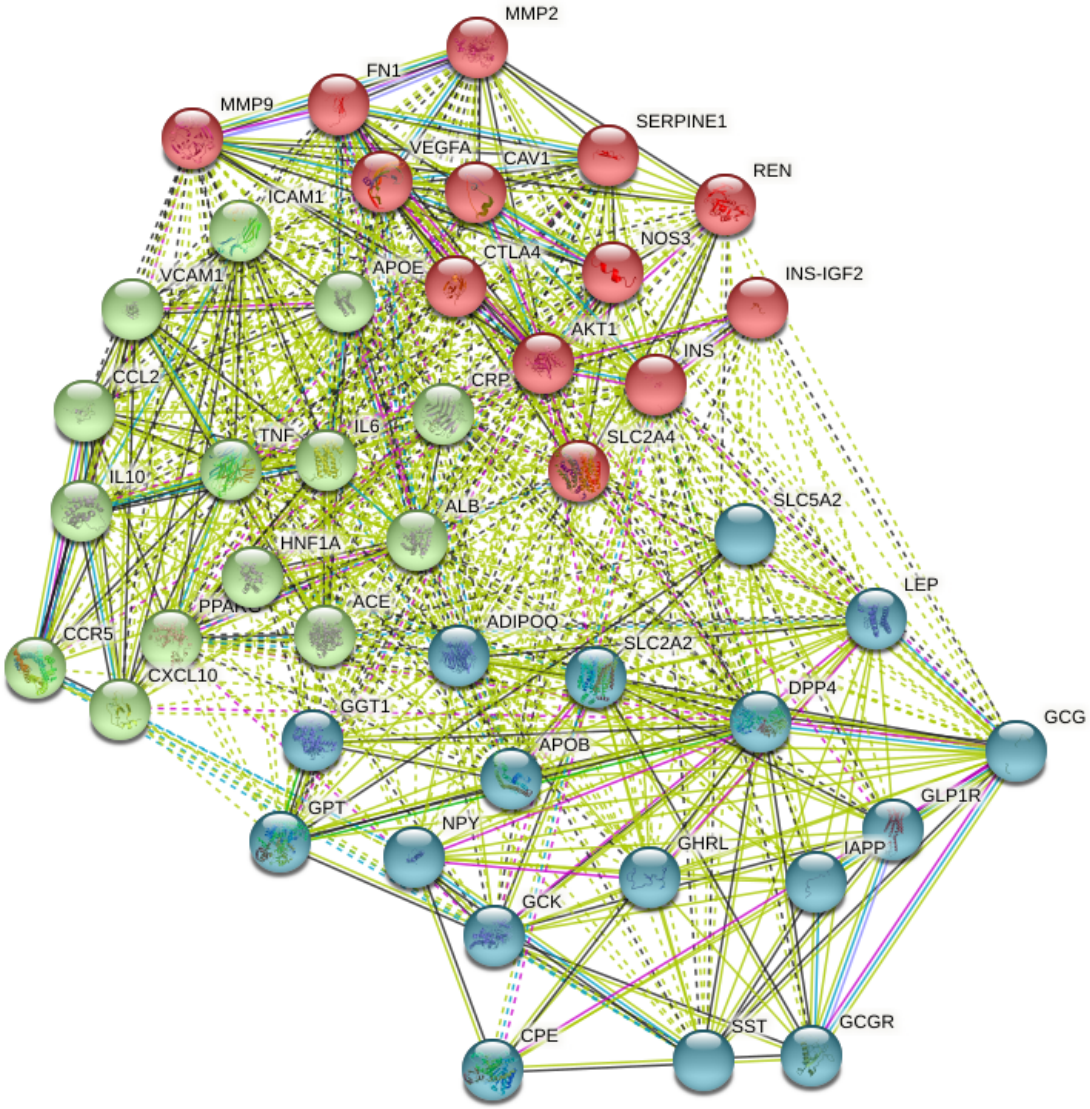

Figure 2

DPP4 related protein module recognition