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Full Length Research Paper

Functional networks for *Salvia miltiorrhiza* and *Panax notoginseng* in combination explored with text mining and bioinformatical approach

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***Salvia miltiorrhiza* (SM) and *Panax notoginseng* (PN) in combination (SMPN) have been widely used primarily in Traditional Chinese Medicine (TCM), for the treatment of coronary heart disease, and its pharmacological activity should be complicated because of its multiple components. Here, we combine text mining with bioinformatics to predict functional networks for the combination. 53 genes related with SMPN were found with text mining. Protein-protein interaction information for these genes from databases and Literature data was searched. Eight highly-connected regions were detected by IPCA algorithm to infer significant complexes or pathways in this network. Over-represented Gene Ontology categories of highly-connected regions by biological network gene ontology tool involved in small GTPase mediated signal transduction, apoptosis, regulation of immune effector process, phosphorylation about enzyme linked receptor protein signaling pathway, positive regulation of biological process. Integrate expression data from six microarray experiments about coronary heart disease into the SMPN network, and use the jActiveModules tool to find active subnetworks in differential expression conditions. The most relevant functions and pathways extracted from these subnetworks were related to proliferation and apoptosis of endothelial cell, apoptosis of arterial smooth muscle cell, apoptosis and regulation of immune system process within macrophages during foam cell formation, cardiocyte apoptosis. Analysis of the subnetwork composition indicated that there were in each subnetworks, and in the most subnetworks were dominant, the nodes came from SM network more than from PN network. It was suggested that, therapeutic efficacies of SMPN should be results of interaction between SM and PN in the multiple pathways and biological processes, and SM maybe play a principal role and PN serve as adjuvant one to assist the effects during the treatment of coronary heart disease.**

Key words: *Panax notoginseng*, *salvia miltiorrhiza*, herbal combination, bioinformatics, text mining, pharamcological activity.

INTRODUCTION

The combination therapy with medical plants (such as Chinese herbal medicine) is used to amplify the therapeutic efficacies and/or reduce adverse effects today (Hu et al., 2009; Garin et al., 2009). The combined treatment with multiple herbs of distinct but related mechanisms has been advocated for thousands of years in Traditional Chinese Medicine (TCM), a unique medical system assisting the ancient Chinese in dealing with disease. Traditional Chinese herb pairs (TCHPs), which are the basic unit in TCM prescriptions called formulae and an intermediate point between single herbs and multi-herb recipes Ung et al., (2007) consist of two relatively standard single herbs. According to Chinese records and the classic books about herbs in China, many TCHPs showed significantly better pharmacological efficacy than when the herbs were used individually, even occurred distinct efficacy Yang et al., (2009). However, the pharmacological mechanisms of most formulae and TCHPs were unclear. Text mining can effectively utilize the large volume of literature, by which

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retrieve knowledge hidden in text and systematically present the distilled knowledge such as the pharmacological mechanism of Traditional Chinese herbs (Fang et al., 2008; Zhou et al., 2010), patterns to users in a concise form. In fact, The therapeutic mechanism of drug whatever hitting single or multiple targets is a biological network comprising hundreds to thousands of protein interactions in various affected tissues and effector cells. Thus, the therapeutic mechanism of drug combination should also be involving the complicate biological network. Systems biology seeks to understand how system properties emerge from the non-linear interactions of multiple components, and the recent progress in systems biology suggests a potential strategy, using computational tools to predict biological networks, can lead to a deeper understanding of complicated system (Gilchrist et al., 2006)

It was validated that *Salvia miltiorrhiza* (SM) and *Panax notoginseng* (PN) in combination against several diseases such as coronary heart disease (Lei and Chiou, 1986). It was well known that both SM and PN have multiple pharmacological mechanisms against diseases (Yu et al., 2008; Ling et al., 2009), but the molecular mechanisms in combination was explained in a biased way. Here, we combine text mining with methods of systems biology, to predict functional networks for SM and PN in combination (SMPN), providing insight into pharmacological mechanisms of SMPN.

METHODS

Text mining

Text mining used TCMGeneDIT (Fang et al., 2008), a database system providing association information about TCMs, genes, diseases, TCM effects and TCM ingredients automatically mined from vast amount of biomedical literature. The database integrating TCMs with life sciences and biomedical studies would facilitate the modern clinical research and the understanding of therapeutic mechanisms of TCMs and gene regulations. Entering '*salvia miltiorrhiza*' and 'panax notoginseng' as the search term in the main search interface of TCMGeneDIT, and then retrieved the information of TCM-Gene, to understand the possible therapeutic mechanisms of SM and PN via gene regulations. The t values greater than 95% were taken as significant.

Protein–protein interaction network

Genes and their product proteins function in a concert rather than isolated manner, proteins interacting with other proteins form modules (e.g. complexes or pathways) to carry out cellular functions. SM and PN regulate some genes expression or proteins activity demonstrated by literatures, and must involve in other genes or proteins interacted data (IntAct) and Molecular Interactions Database (MINT), and complemented with curated relationships parsed from literature using Agilent literature search.

These datasets are mostly based on experimental evidence. We did not include data that were deemed to be of lower quality. This protein–protein interaction network was visualized using cytoscape (Shannon et al., 2003).

Highly-connected regions of the network

In order to better understand our complicated network, we used PICA algorithm to obtain motifs (modules) of highly interconnected regions. The IPCA algorithm can detect densely connected regions in the interactome network (Li et al., 2008). Interactomes with a score greater than 2.0 and at least four nodes were taken as significant predictions.

Mapping gene expression to the interaction network

Identifying motifs (modules) to understand the network of interactions among biomolecules is still a central challenge in current systems biology, usually associated with high false positive and false negative rates (Jung et al., 2010; Liu et al., 2009; Wang et al., 2010). Taking the closely-connected and co-expressed differential genes in the condition-specific network as the signatures of the underlying responsive gene modules provides a new strategy to solve the module identification problem (Gu et al., 2010). In this study, six microarray experiments to identify the active module of the interaction network were analyzed. The experimental data were from the Gene Expression Omnibus (GEO), and the statistical software R was used for analysis. The expression level for a gene was associated with a corresponding protein in the interaction network. The jActiveModules was used to find a high scoring network for each condition. This software employed a published z-scores of expression change algorithm (Ideker et al., 2002), which consisted of a network scoring metric and a network search function. For a given network, the network score was computed as a standardized weighted average of the z-scores for the individual network nodes. Parameter values used to initialize the algorithm were Start Temp=2.0, End Temp=0.01, Iterations=10^6 and Hubs=10.

Gene ontology analysis

Gene ontology (GO) is a widely used gene functional categorization system. To identify the function of each cluster generated by IPCA individually, GO clustering analysis was performed with the proteins described in all subnetworks. For this purpose, the latest version of Biological Network Gene Ontology (BiNGO) tool (Maere et al., 2005) was used to statistically evaluate groups of proteins with respect to the existing annotations of the Gene Ontology Consortium (GOC). The degree of functional enrichment for a given cluster was quantitatively assessed (P value) by hypergeometric distribution, implemented in BiNGO tool. We selected the 10 GO biological categories with the smallest P values as significant.

Network comparison

Used graph merge tool to compare between the networks. This tool can find intersection or difference between networks based on node/edge attributes (Shannon et al., 2003). ID mapping were utilized for comparing networks. Set operation: intersection.

RESULTS

Effector genes of *salvia miltiorrhiza* and *Panax notoginseng*

The text mining results indicated SM and PN associated with 21 genes, 41 genes, respectively, including 9 overlap

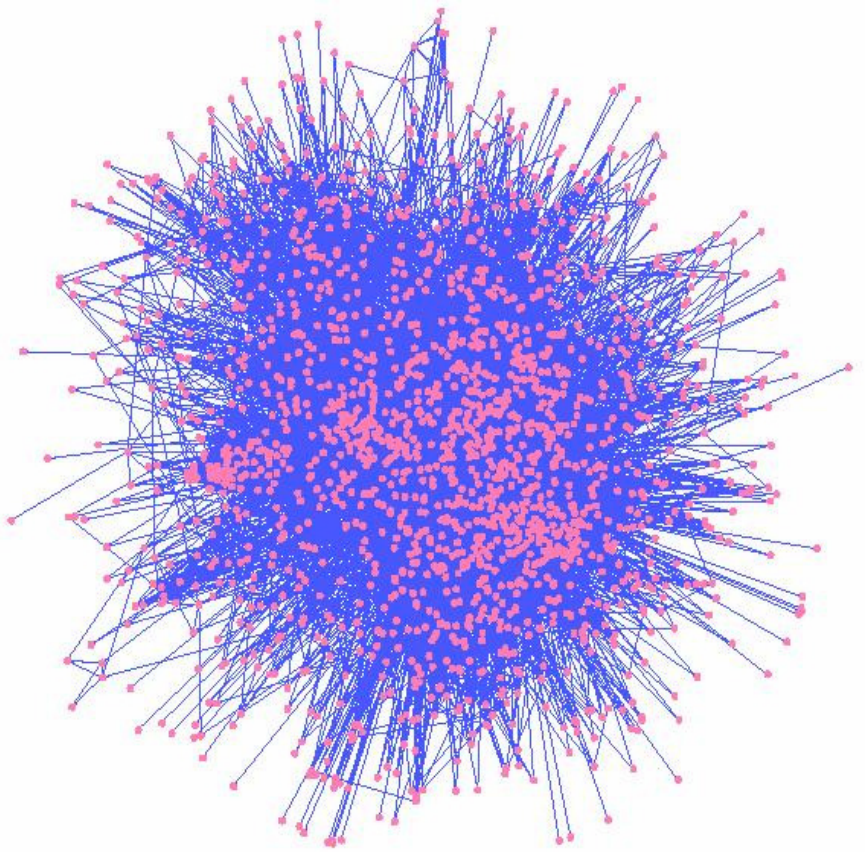

Figure 1. Protein–protein interaction network about mechanisms of SMPN. Cycles represent nodes. All edges represent interactions between the nodes.

genes (data not shown), which deduced that 53 genes associated with SMPN.

Biological network

With the available data regarding interactions between different human proteins, we searched for protein partners for the genes associated with SM, PN and SMPN by the nearest-neighbor expansion method, and obtained three PPI networks, containing 1480 human proteins (nodes) and 13186 interactions (edges) (data not shown), 887 nodes and 8530 edges (data not shown), 1716 nodes and 16954 edges (Figure 1), respectively.

Analysis of the SMPN network features

In order to better understand functions of the SMPN network, eight significantly highly-connected regions (or clusters) (that is, score 2 is significant; it represents the log of the probability that the network was found by chance) were proposed by IPCA, a clustering algorithm for analysis of protein interaction network topological structure, so that infer significant complexes or pathways. These subnetworks of highly-connected regions were visualized by cytoscape (Figure 2).

BiNGO tools were used to statistically evaluate groups of genes with respect to the present annotation categories of the GOC. The most relevant functions and pathways extracted from these subnetworks were related to small GTPase mediated signal transduction, mRNA process, transcription, apoptosis, regulation of immune effector process, phosphorylation about enzyme linked recptor protein signaling pathway, positive regulation of ubiquitin-protein ligase activity, positive regulation of biological process (Table 1).

Mapping gene expression to the SMPN network

Integration of protein interactions with widely available mRNA expression data uncovers some functions of the SMPN. The SMPN is used to against coronary heart disease, so we selected six micro array experiments that were designed with respect to pathological models of

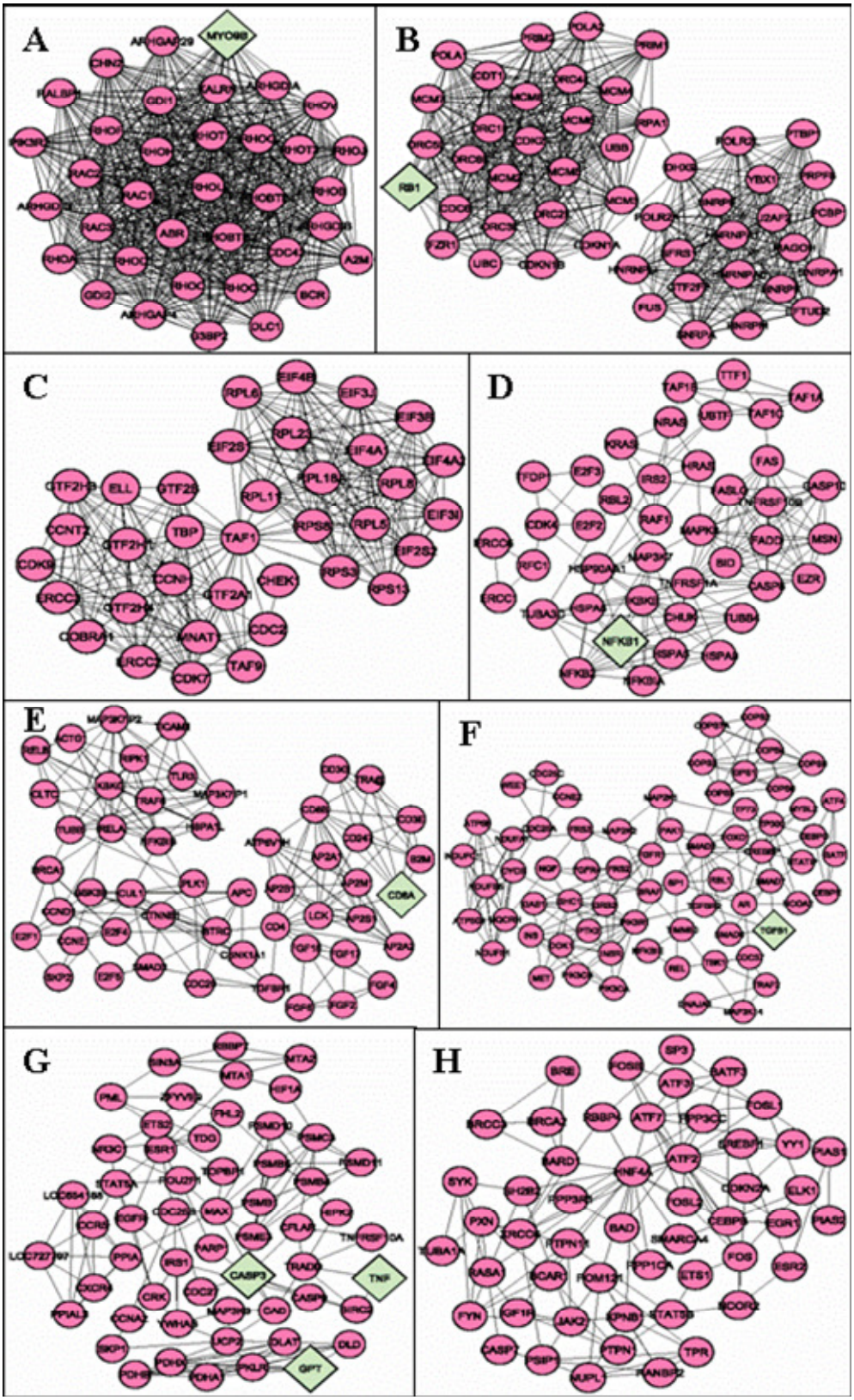

Figure 2. The subnetworks made up of highly-connected regions. Diamonds represent seed node. Cycles represent neighbor nodes. All edges represent interactions. (A) cluster 1, (B) cluster 2, (C) cluster 3, (D) cluster 4, (E) cluster 5, (F) cluster 6, (G) cluster 7, (H) cluster 8.

Table 1. The biological categories of the subnetworks made up of highly-connected regions.

Cluster	ID	Description	p-value
Cluster 1	7264	Small GTPase mediated signal transduction	1.07E-41
	7242	Intracellular signaling cascade	2.76E-33
	7165	Signal transduction	7.00E-22
	7154	Cell communication	2.03E-20
	7266	Rho protein signal transduction	9.47E-20
	7265	Ras signal transduction	1.45E-16
	51244	Regulation of cellular process	1.65E-11
	50791	Regulation of biological process	4.21E-11
	65007	Biological regulation	2.58E-10
	7010	Cytoskeleton organization and biogenesis	7.24E-10
Cluster 2	6374	Nuclear mRNA splicing, via spliceosome	6.00E-30
	375	RNA splicing, via transesterification reactions	6.00E-30
	377	RNA splicing, via transesterification reactions	6.00E-30
	6270	DNA replication initiation	6.42E-25
	6395	RNA splicing	2.92E-24
	6260	DNA replication	1.22E-23
	6397	mRNA process	2.07E-23
	6139	nucleobase, nucleoside, nucletide and nucleic	5.42E-23
	16071	mRNA metabolic process	3.41E-22
	6263	DNA-dependent DNA replication	4.81E-22
Cluster 3	44249	cellular biosynthetic process	9.01E-32
	6368	RNA elongation from RNA polymerase II promoter	1.95E-29
	6354	RNA elongation	5.80E-29
	6367	Transcription initiation from RNA polymerase II promoter	7.95E-25
	6352	Transcription initiation	1.37E-23
	9059	Macromolecule biosynthetic process	1.27E-22
	6366	Transcription from RNA polymerase II promoter	9.13E-21
	10467	Gene expression	1.17E-20
	9058	Biosynthetic process	6.13E-20
	6351	Transcription, DNA-dependent	2.23E-19
Cluster 4	8633	Activation of pro-apoptotic gene products	5.20E-14
	8624	Induction of apoptosis by extracellular signals	8.17E-12
	51242	Positive regulation of cellular process	3.64E-11
	6915	Apoptosis	5.62E-11
	12501	Programmed cell death	6.31E-11
	48518	Positive regulation of biological process	1.87E-10
	16265	Death	2.80E-10
	8219	Cell death	2.80E-10
	8632	Apoptotic program	5.93E-09
	42981	Regulation of apoptosis	6.42E-09
Cluster 5	50690	Regulation of defense response to virus by virus	3.41E-17
	50688	Regulation of defense response to virus	2.69E-14
	43900	Regulation of multi-prganism process	4.78E-14
	48518	Positive regulation of biological process	4.93E-14
	51242	Positive regulation of cellular process	6.37E-14
	2831	Regulation of response to biotic stimulus	1.32E-13

Table 1. Contd.

	2697	Regulation of immune effector process	4.63E-13
	2682	Regulation of immune system process	6.74E-13
	7167	Enzyme linked receptor protein signaling pathway	5.21E-11
	48583	Regulation of response to stimulus	1.94E-10
	6796	Phospate metabolic process	4.08E-20
	6793	Phosphorus metabolic process	4.08E-20
	16310	Phosphorylation	5.22E-19
	7167	Enzyme linked recptor protein signaling pathway	2.08E-17
Cluster 6	7169	Transmembrance receptor protein tyrosine kinase	2.88E-14
	43687	Post-translational protein modification	1.72E-13
	43549	Regulation of kinase activity	1.33E-12
	51338	Regulation of transferase activity	1.77E-12
	45859	Regulation of protein kinase activity	1.80E-11
	65009	Regulation of molecular function	1.84E-11
	43085	Positive regulation of catalytic activity	2.21E-14
	51437	Positive regulation of ubiquitin-protein ligase activity	1.53E-12
	51443	Positive regulation of ubiquitin-protein ligase activity	1.77E-12
	51439	Regulation of ubiquitin-protein ligase activity	2.34E-12
Cluster 7	51351	Positive regulation of ligase activity	2.69E-12
	51438	Regulation of ubiquitin-protein ligase activity	4.55E-12
	51340	Regulation of ligase activity	6.63E-12
	51436	Negative regulation of ubiquitin-protein ligase activity	5.25E-11
	31145	Anaphase-promoting complex-dependent proteasome	5.25E-11
	51352	Negative regulation of ligase activity	6.00E-11
	48518	Positive regulation of biological process	5.18E-13
	51252	Regulation of RNA metabolic process	4.89E-11
	19219	Regulation of nucleobase, nucleoside, nucleotide	6.04E-11
	19222	Regulation of metabolic process	6.95E-11
Cluster 8	31323	Regulation of cellular metabolic process	2.19E-10
	51242	Positive regulation of cellular process	5.45E-10
	60255	Regulation of macromolecule metabolic process	8.62E-10
	6355	Regulation of transcription, DNA-dependent	1.71E-09
	10556	Regulation of macromolecule biosynthetic process	4.64E-09
	9889	Regulation of biosynthetic process	5.92E-09

endothelial cells, vascular smooth muscle cells, macrophage and ischemic myocardium (Table 2). Integrate expression data in these experiments into the SMPN interaction network. We used the jActiveModules tool to find active subnetworks in differential expression conditions. The highest scoring network for each condition was shown as Figure 3. The SMPN maybe play a role, in positive regulation of cellular process and response to stress during human umbilical vein endothelial cells treated with Leukotriene D4 and Thrombin, in regulation of proliferation and apoptosis of human endothelial cell while exposed to shear stress and TNF, in apoptosis of arterial smooth muscle cells while exposed to a broad range of oxygen, in regulation of apoptosis and positive regulation of immune system process within macrophages during foam cell formation, in positive regulation of cellular process and apoptosis within ischemic myocardium (Table 3).

Analysis of the subnetwork composition

In order to understand SM network and PN network contributions to the subnetworks (the clusters and the modules), use graph merge program to identify where the nodes in the subnetworks come from. In each subnetworks, there were some nodes came from intersection between SM network and PN network, and in

Table 2. Summary of the micro array experiments used in our analysis.

ID	Description	Sample
GSE3589	Leukotriene D4- and thrombin-triggered transcriptomes in human umbilical vein endothelial cells	21
GSE1518	Human endothelium exposed to shear stress and pressure	8
GSE2638	HMEC gene profile after TNF-stimulation	6
GSE4725	Hypoxia	6
GSE7138	Induction of dendritic cell-like phenotype in macrophages during foam cell formation	22
GSE5406	Human ischemic cardiomyopathy, idiopathic cardiomyopathy, and nonfailing controls	336

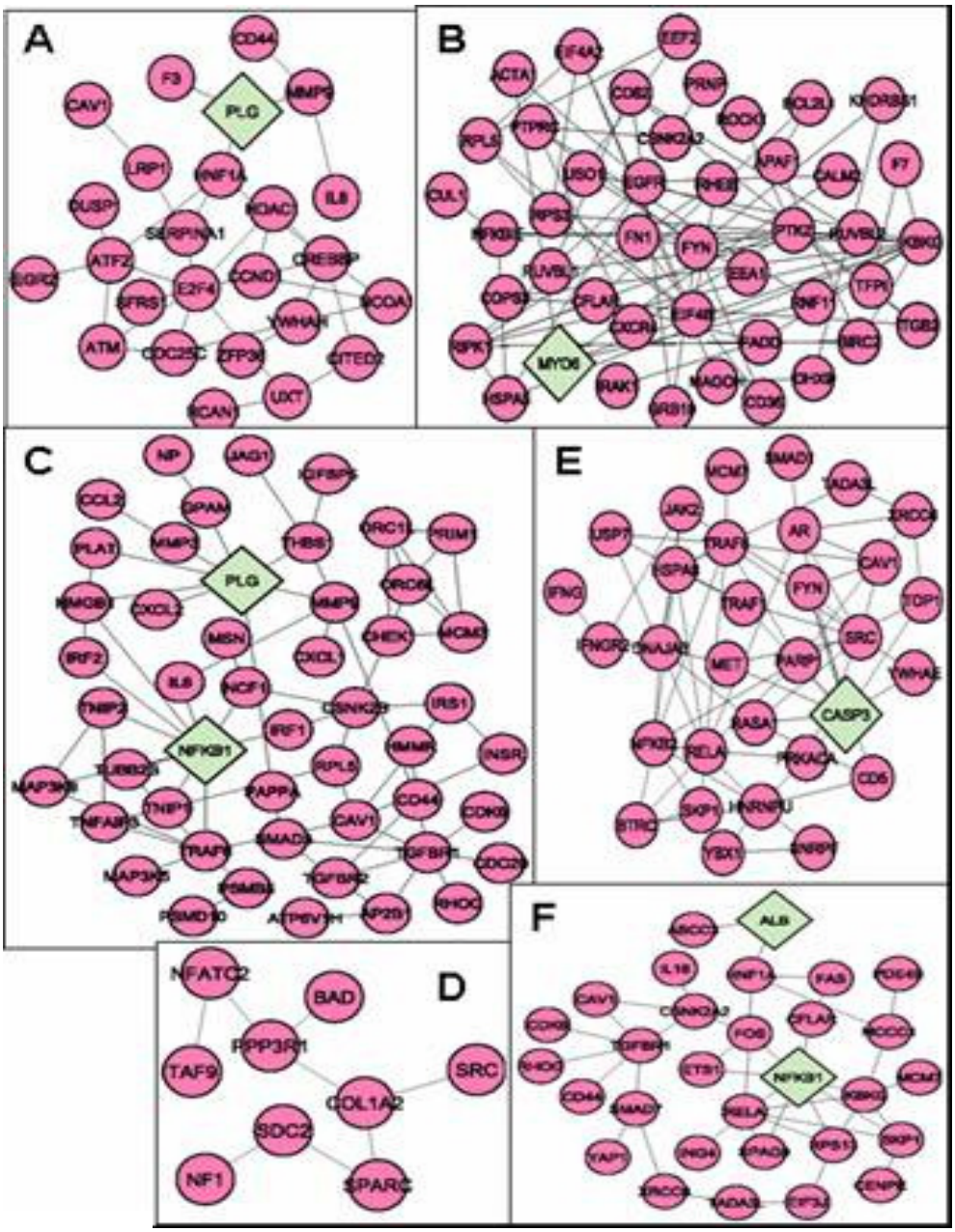

Figure 3. Modules of the SMPN network under different conditions. Diamonds represent seed node. Cycles represent neighbor nodes. All edges represent interactions. (A) shear, (B) thombin and LDT4, (C) TNF, (D) Ischemia, (E) Oxidize LDL, (F) Hypoxia.

Table 3. The biological categories of the Modules under different conditions.

Cluster	ID	Description	P-value
Shear	50852	T cell receptor signaling pathway	1.73E-06
	42981	Regulation og apoptosis	9.09E-06
	43067	Regulation of programmed	1.02E-05
	50851	Antigen receptor-mediated signaling pathway	1.14E-05
	6915	Apoptosis	2.05E-05
	12501	Programmed cell death	2.20E-05
	2429	Immune response-activating cell surface receptor	2.68E-05
	2768	Immune response-activating cell surface receptor	3.09E-05
	2757	Immune response-activating transduction	4.05E-05
	44419	Interspecies interation between organisms	4.07E-05
Thombin and LDT4	48518	Positive regulation of biological process	8.15E-06
	6950	Response to stress	2.22E-05
	10604	Positive regulation of macromolecule metabolic process	5.25E-05
	31325	Positive regulation of cellular metabolic process	7.69E-05
	9893	Positive regulation of metabolic process	8.61E-05
	45941	Positive regulation of transduction	1.51E-04
	10628	Positive regulation of gene expression	1.68E-04
	51093	Negative regulation of developmental process	1.78E-04
	45935	Positive regulation of nucleobase, necleoside,	2.05E-04
	51242	Positive regulation of cellular process	2.07E-04
TNF	42127	Regulation of cell proliferation	2.82E-08
	50793	Regulation of developmental process	9.29E-08
	48518	Positive regulation of biological process	2.21E-07
	48523	Negative regulation of cellular process	8.58E-07
	43085	Positive regulation of catalytic process	8.74E-07
	51242	Positive regulation of cellular process	2.38E-06
	8285	Negative regulation of cell proliferation	1.04E-05
	42981	Regulation of apoptosis	2.94E-05
	65009	Regulation of molecular function	3.07E-05
	43067	Regulation of programmed cell death	3.27E-05
Ischemia	48518	Positive regulation of biological process	1.13E-08
	51242	Positive regulation of cellular process	3.44E-07
	51093	Negative regulation of developmental process	2.91E-06
	50793	Regulation of developmental process	1.79E-05
	43066	Negative regulation of apoptosis	6.83E-05
	43069	Negative regulation of programmed cell death	7.30E-05
	10468	Regulation of gene expression	8.68E-05
	9889	Regulation of biosynthetic process	8.96E-05
	6916	Ant-apoptosis	2.31E-04
	31323	Regulation of cellular metabolic process	2.33E-04
Oxidize LDL	7243	Protein kinase cascade	7.82E-08
	42981	Regulation of apoptosis	7.96E-06
	43067	Regulation of programmed cell death	8.80E-06
	50793	Regulation of develomental process	2.40E-05
	48518	Positive regulation of biological process	7.20E-05
	43170	Macromolecule metabolic process	9.27E-05

Table 3. Contd.

	44419	Interspecies interaction between organisms	1.13E-04
	50852	T cell receptor signaling pathway	1.57E-04
	2684	Positive regulation of immune system process	1.60E-04
	51251	Positive regulation of lymphocyte activation	2.26E-04
Hypoxia	8633	Activation of pro-apoptotic gene product	6.44E-05
	7169	Transmembrane receptor protein tyrosine kinase	1.44E-04
	43065	Positive regulation of apoptosis	3.87E-04
	43068	Positive regulation of programmed cell death	4.01E-04
	7167	Enzyme linked receptor protein signaling pathway	4.06E-04
	21896	Forebrain astrocyte differentiation	6.19E-04
	21897	Forebrain astrocyte development	6.19E-04
	48715	Negative regulation of oligodendrocyte differention	6.19E-04
	48745	Smooth muscle development	6.19E-04
	31214	Biomineral formation	8.76E-04

Table 4. SM network and PN network contributions to the subnetworks.

	Total	From PN (%)	Intersection (%)	From SM (%)
Cluster 1	36	22 (61)	9 (25)	5 (14)
Cluster 2	48	14 (29)	24 (50)	10 (21)
Cluster 3	36	2 (6)	14 (39)	20 (55)
Cluster 4	41	2 (5)	29 (71)	10 (24)
Cluster 5	51	4 (8)	25 (49)	22 (43)
Cluster 6	67	5 (8)	31 (46)	31 (46)
Cluster 7	56	2 (4)	26 (46)	28 (50)
Cluster 8	51	2 (4)	25 (49)	24 (48)
Shear	44	3 (7)	26 (59)	15 (34)
Thombin	25	4 (16)	14 (56)	7 (28)
TNF	49	10 (20)	21 (43)	18 (37)
Ischemic	30	2 (7)	16 (53)	12 (40)
Macrophage	31	0	23 (74)	8 (26)
SMC	9	1 (11)	3 (33)	5 (56)

the most subnetworks were dominant (Table 4), which suggested that functions of the subnetworks should be results of interaction between SM and PN. The nodes in the most subnetworks came from SM network (Table 4), represented that SM maybe play a principal role and PN serve as adjuvant to assist the effects.

DISCUSSION

SMPN has been used primarily in TCM for the treatment of coronary heart disease, a chronic disease that coronary artery stenosis because of atherosclerosis cause myocardial ischemia. The pathophysiology of coronary heart diseases involve in dysfunction and proliferation and apoptosis of endothelial cell (Levade et al., 2001), inflammatory cell infiltration, accumulation of lipids, macrophages forming foam cell and apoptosis (Hagg et al., 2009), migration and proliferation and apoptosis of smooth muscle cell (Pavoine and Pecker, 2009), cardiocyte apoptosis (Lafontant and Field, 2006). Linked to the therapeutic efficacies of SMPN, previous studies have revealed that the cellular mechanisms involve in inhibition of adenosine diphosphate-induced platelet aggregation (Yao et al., 2008), inhibition of adhesion molecule expression in human vascular endothelial cells (Ling et al., 2008) and altering the arterial myogenic response (Baek et al., 2009). However,

the biological actions of single SM or PN have also revealed that involved in more wide mechanisms. For example, the biological mechanisms of SM still associated with Ras signal transduction apoptosis (Che et al., 2009) and proliferation (Chor et al., 2005), the same to PN (Gao et al., 2007; Hai et al., 2007; Wang et al., 2009). Therefore, it was presented that interactions between SM and PN should involve in further pathways and biological processes. In this study, a complicated network for pharmacological mechanisms of SMPN was predicted using information from literatures and computational tools of systems biology. To understand this network, motifs (modules) of highly interconnected regions were identified by graph-theoretic clustering method. Over-represented GO categories of motifs involved in small GTPase mediated signal transduction, phosphorylation about enzyme linked recptor protein signaling pathway, apoptosis, regulation of immune effector process, positive regulation of ubiquitin-protein ligase activity, and positive regulation of biological process.

It was known that combining expression and GO data, can overcome the noise form data, and then generate some specific and testable predictions (King et al., 2005). In the present study, integrate expression data from six micro array experiments about coronary heart disease into the SMPN network, and use the jActiveModules tool to find active subnetworks in differential expression conditions. The most relevant functions and pathways extracted from these subnetworks were related to proliferation and apoptosis of endothelial cell, apoptosis of arterial smooth muscle cell, apoptosis and regulation of immune system process within macrophages during foam cell formation, cardiocyte apoptosis. Therefore, it was suggested that the therapeutic mechanisms of SMPN against coronary heart disease were likely to associate with multiple pathways and biological processes, including intracellular Ras signal transduction，apoptosis and proliferation of effector cell, regulation of immune effector process at least. The comparison between subnetworks (motifs/modules) indicated that some nodes in each subnetworks came from intersection between SM network and PN network, which suggested that therapeutic efficacies of SMPN should be results of interaction between SM and PN. In TCM, SM is as principal component and PN serve as an adjuvant one to assist the effects during the treatment of coronary heart disease, which is partly supported by the result by analysis of the subnetwork composition that the nodes in the most functional subnetworks came from SM network more than from PN network in this study.

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