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Target Network Analysis of Adiponectin, a Multifaceted Adipokine

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ABSTRACT

Application of network analysis to dissect the potential molecular mechanisms of biological processes and complicated diseases has been the new trend in biology and medicine in recent years. Among which, the protein–protein interactions (PPI) networks attract interests of most researchers. Adiponectin, a cytokine secreted from adipose tissue, participates in a number of metabolic processes, including glucose regulation and fatty acid metabolism and involves in a series of complicated diseases from head to toe. Hundreds of proteins including many identified and potential drug targets have been reported to be involved in adiponectin related signaling pathways, which comprised a complicated regulation network. Therapeutic target database (TTD) provides extensive information about the known and explored therapeutic protein targets and the signaling pathway information. In this study, adiponectin associated drug targets based PPI was constructed and its topological properties were analyzed, which might provide some insight into the dissection of adiponectin action mechanisms and promote adiponectin signaling based drug target identification and drug discovery. J. Cell. Biochem. 114: 1145–1152, 2013.

KEY WORDS: ADIPONECTIN; NETWORK ANALYSIS; SUCCESSFUL DRUG TARGET; CLINICAL TRIED DRUG TARGET; RESEARCH DRUG TARGET

As is well known, each cell's behavior is a consequence of the complex interactions among its numerous constituents, such as DNA, RNA, proteins, metabolites, and other small molecules [Albert, 2005] which assembles a series of complicated networks. The study of these networks is becoming increasingly useful to understanding and dissecting the complicated process of biological systems. With the advances of genomics, transcriptome, proteomics, metabolomics, and system biology, the study of biological systems with network view has been attracted emphasis among biologists. Today's biological studies have entered an era of network analysis which has several levels from DNA to protein. Among which, the protein–protein interaction networks (PPIs) developed really rapidly in recent years. Establishment of PPIs and using them to improve the analysis and prediction of various biological informations have been reported by a series of previous papers [Chou and Cai, 2006; Hu et al., 2011ab; Huang et al., 2011a; Li et al., 2012]. As early as in Chou and Cai [2006] established a predictor called "GO-PseAA" to predict PPIs from sequences in a hybridization space. Recently, Huang and his colleagues developed a new computational method to predict the transcriptional activity for one-, two-, three-, and four-site p53 mutants [Huang et al., 2011b]. The same group also developed a network-based method to predict body fluids where proteins are secreted into [Hu et al., 2011b] and use maximum relevance minimum redundancy (mRMR) approach and shortest path in PPI to identify colorectal cancer related genes [Li et al., 2012]. The topological analysis of PPIs has also been considered as a useful tool for predicting, identifying, and prioritizing drug-target [Ruffner et al., 2007; Klipp et al., 2010], understanding of the pathophysiology of complicated diseases such as cancer [Kusunoki et al., 2010], diabetes and Alzheimer's disease [Liu et al., 2012], predicting the subcellular locations of proteins [Hu et al., 2012], predicting of human genes' regulatory functions [Gao et al., 2012], and so on.

Adiponectin, an adipose tissue secreted hormone, has been studied intensively for the past decade mainly due to its important roles in obesity [Behre, 2007], inflammation [Robinson et al., 2011],

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diabetes [Han et al., 2009], cardiovascular diseases [Hui et al., 2012], cancer [Chen and Wang, 2011], kidney diseases [Guebre-Egziabher et al., 2007], etc. There have been more than 4,200 publications in PubMed as searching with "adiponectin" in title which increased quickly day by day. Accumulated data have revealed that adiponectin is a beneficial adipokine with multiple bioactivities from head to toe [Brochu-Gaudreau et al., 2010]. Underlying these multifaceted actions, a large number of proteins including receptors, adaptors, binding proteins for adiponectin have been identified [Buechler et al., 2010]. Definitely, interactions among these proteins could comprise complicated PPI networks. However, no network analysis on these proteins has been performed yet. In the present study, the networks for adipoenctin associated target based proteins have been constructed and their topological properties have been described based on the therapeutic target database (TTD).

METHODS

To establish a really useful analysis method or statistical predictor for a protein system, a series of previous studies have proposed some practical procedures [Lin et al., 2011; Wu et al., 2011; Wang et al., 2011b; Chou et al., 2012]. In this paper, the construction and analysis of adiponectin associated drug target based PPI was developed by integrating these methods and application of open source softwares. Dataset for adiponectin and adiponectin associated targets were retrieved and extracted from NCBI's Entrez and TTD (http://bidd.nus.edu.sg/group/ttd/ttd.asp). Adiponectin associated interaction information was retrieved from NCBI's Entrez Gene in June 1, 2012 using the keywords "adiponectin," "ADIPOQ," "C1Q and collagen domain containing," "ACDC," "ACRP30," "ADIPQTL1," "ADPN," "APM-1," "APM1," and "GBP28." The retrieved results including *Homo sapiens* were selected. The corresponding each gene expression product-protein was confirmed. All the adiponectin associated proteins were imported to TTD (http://bidd.nus.edu.sg/group/ttd/ttd.asp) to identify its potentials as drug targets. TTD is a database designed to provide information about the known and explored therapeutic protein and nucleic acid targets, the targeted disease, the signaling pathways information and the corresponding drugs directed at each of these targets. In TTD, there are three classes of drug targets, successful drug target, clinical drug target, and experimental drug targets [Zhu et al., 2010]. The genes of verified drug targets were further imported into InterologFinder to retrieve known PPIs. InterologFinder is designed to retrieve PPI from both known and predicted PPI data sets using data from the National Center for Integrative Biomedical Informatics (NCIBI)'s Michigan molecular interactions (MiMI) which contains data from IntAct, DIP, BIND, and others. Experimentally determined interactions between submitted proteins and all other proteins were included while predicted interactions between submitted proteins and all other proteins were excluded. To confirm the quality of this data set, this database has been carefully compared with other databases STITCH and KEGG, as well as the literature.

Cytoscape, an open source software platform for visualizing complex networks and integrating these with any type of attribute data, was used to construct and visualization of the target networks. Cytoscape are available for download from http://www.cytoscape.org/. NetworkAnalyzer (http://chianti.ucsd.edu/cyto_web/plugins/index.php), a cytoscape plugin, was used to analyze the constructed networks. NetworkAnalyzer performs analysis of biological networks and calculates network topology parameters including the diameter of a network, the average number of neighbors, and the number of connected pairs of nodes. It also computes the distributions of more complex network parameters such as node degrees, average clustering coefficients, topological coefficients, and shortest path lengths. It displays the results in diagrams, which can be saved as images or text files. CytoHubba (http://chianti.ucsd.edu/cyto_web/plugins/index.php), a cytoscape plugin, was used to explore important nodes/hubs and fragile motifs in the networks by the topological algorithm degree. Other topological algorithms including edge percolated component (EPC), maximum neighborhood component (MNC), density of maximum neighborhood component (DMNC), maximal clique centrality (MCC), and centralities based on shortest paths, such as bottleneck (BN), eccentricity, closeness, radiality, betweenness, and stress were used for reference.

RESULTS AND DISCUSSION

ADIPONECTIN ASSOCIATED GENE/PROTEIN/TARGETS

By searching NCBI's Entrez Gene in June 1, 2012, 505 relate genes for adiponectin were obtained. Among which, 168 were from *H. sapiens*. Seven genes are adiponectin, circulating adiponectin, repeated results and discontinued genes which were excluded from the study. TTD, a database established in 2002 [Chen et al., 2002], aims to provide information about the known and explored therapeutic targets, the targeted disease, pathway information and the corresponding drugs directed at each of these targets. After two updates, it currently contains 2,025 targets, including 364 successful, 286 clinical trial, 44 discontinued and 1,331 research targets, 17,816 drugs, including 1,540 approved, 1,423 clinical trial, 14,853 experimental drugs and 3,681 multi-target agents (14,170 small molecules and 652 antisense drugs with available structure or oligonucleotide sequence) [Zhu et al., 2010, 2012]. Recently, TTD has been used for drug target analysis, drug research and discovery analysis and drug screening. Chen et al. by comparing target and non-target protein sequences compiled from the TTD, DrugBank, and PFam TTD found that drug targets, like drugs, also display shared features and have a likeness [Chen et al., 2007a]. It was also used to predict the trends and analyze the difficulties in the exploration of therapeutic targets for the treatment of endocrine, metabolic, and immune disorders [Chen et al., 2007b]. In addition, TTD provided potential targets and drugs for future personalized treatment of colorectal cancer in a genome-wide study [Jasmine et al., 2012]. In TTD, drug targets have been classified into four main categories: successful targets, clinical trial targets, research targets, and discontinued targets. In this study, adiponectin associated drug targets were explored from TTD. After retrieving from TTD, 80 drug targets were confirmed: 16 proteins are confirmed as successful drug targets, 20 are clinical trial targets, 43 are research targets, and 1 discontinued target. The other 81 proteins are non-target proteins.

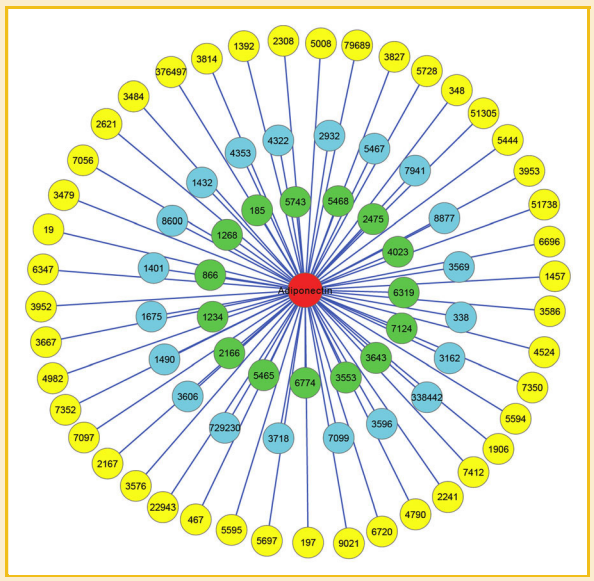

Fig. 1. Adiponectin associated drug targets. Among all the adiponectin associated proteins 16, 20, and 43 proteins are confirmed as successful drug targets (green), clinical trial targets (blue), and research targets (yellow), respectively in TTD. Gene ID numbers were used to represent the targets.

The associated targets (successful drug target, clinical trial target, and research target) are shown in Figure 1.

CONSTRUCTION OF TARGET ASSOCIATED REGULATORY NETWORKS

InterologFinder is designed to retrieve PPIs from both known and our predicted PPI data sets. Prediction of PPI across five species (human, mouse, fly, worm, and yeast) could be easily obtained from InterologFinder [Wiles et al., 2010]. Target based PPI data retrieved from InterologFinder were integrated using Cytoscape version 2.8.2 to model the network. Totally, four networks (successful targets network (STN), clinical trial targets network (CTTN), research targets network (RTN), total targets network (TTN), were constructed and shown as Figure 2.

TOPOLOGICAL PROPERTIES OF THE NETWORKS

It has demonstrated that topological properties of PPI networks are useful to characterize proteins functions [Sharan and Ideker, 2006], to understand molecular mechanisms of diseases [Wang et al., 2011a; Zhang et al., 2011], to explore potential drug targets [Zhu et al., 2009], and to design drug in future [Hase et al., 2009]. To address the topological properties of the four networks, NetworkAnalyzer, a plugin for cytoscape, was used. NetworkAnalyzer is a standard Cytoscape tool for comprehensive network topology analysis [Doncheva et al., 2012] and it computes and displays a comprehensive set of topological parameters, which includes the number of nodes, edges, and connected components, the network diameter, radius, density, centralization, heterogeneity, and clustering coefficient, the characteristic path length, and the distributions of node degrees, neighborhood connectivities, average clustering coefficients, and shortest path lengths [Assenov et al., 2008]. In this study, the topological properties are visualized for STN (Fig. 3A), CTTN (Fig. 3B), RTN (Fig. 3C), and TTN (Fig. 3D) in Figure 3, and are listed in Table I. Node degree distribution was used to distinguish between random and scale-free network topologies. For the four networks, the degree distribution of the proteins in each network decreases following a power-law (P(k), kc where k is the number of partner proteins). This suggested that these networks, like other biological networks, demonstrating scale-free properties. The network diameter is the largest distance between two nodes and the characteristic path length gives the expected distance between two connected nodes. The CTTN have the biggest network diameter and longest characteristic path length. The average number of neighbors indicates the average connectivity of a protein in the network. On average, proteins in TTN have 2.961 interaction partners, a little higher than the other three networks. A normalized version of this parameter is the network density showing how densely the network is populated with edges. As expected, the TTN has the smallest network density while the STN has the highest. Network centralization, another related parameter to network density demonstrated similar results suggesting that the STN network showed the most centralized topological structure. The average clustering coefficient is the average of the clustering coefficients for all the proteins to form clusters in the network. The average clustering coefficient decreases as the number of protein interactions increases, because sparsely connected proteins are neighbors of highly connected proteins (hub proteins) [Kar et al., 2009]. In the four networks, the STN has lower clustering coefficient suggesting more protein interactions while the CTTN has the clustering coefficient 0 suggesting that there is no connection at all between these nodes in CTTN. Also, these parameters are visualized as Figure 3.

HUBBA ANALYSIS ADIPONECTIN ASSOCIATED TARGET NETWORKS

Hub Objects Analyzer (Hubba) is a web-based service for exploring important nodes in an interactome network generated from specific small- or large-scale experimental methods based on graph theory [Lin et al., 2008]. To explore the important nodes in the adiponectin related PPI networks, we further performed Hubba analysis. The results for STN, CTTN, and RTN were shown in Figure 4. The top five nodes in highest ranking are listed as Table II.

As a multiple bioactive adipokine, several potential targets for adiponectin have been identified and proposed such as adiponectin receptors (AdipoR1 and AdipoR2) [Kadowaki and Yamauchi, 2005; Heiker et al., 2010; Kim et al., 2010], AMPK [Shibata et al., 2005; Heiker et al., 2010; Iwabu et al., 2010], PPARα [Heiker et al., 2010], and so on. However, there is no clinical and experimental drug available for adiponectin receptors at present. Both receptors are 7-transmembrane proteins but showed unique structures with an internal N-terminus and an external C-terminus, which is opposite to the topology of G-protein coupled receptors. Also, recent findings have identified several binding proteins such as CK2b, ERp46, and RACK1 for these receptors [Buechler et al., 2010], which raise several key questions to be answered before they became successful drug targets. The Hubba analysis revealed that in the adiponectin

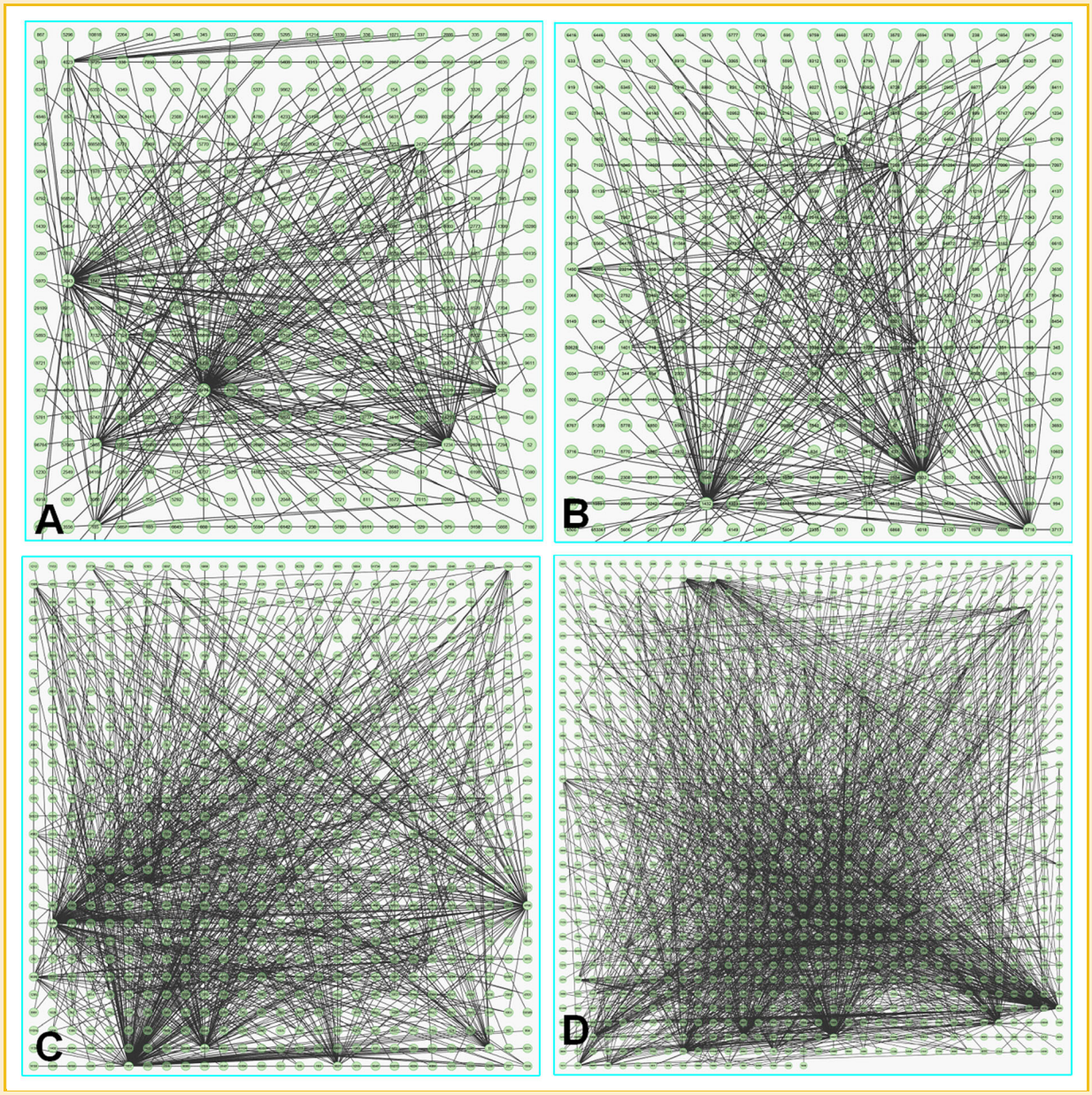

Fig. 2. The drug target proteins based networks for adiponectin. A: successful drug targets network (STN); (B) clinical trial targets network (CTTN); (C) research targets network (RTN); (D) total targets network (TTN).

associated successful drug target networks, signal transducer and activator of transcription 3 (STAT3), insulin receptor (INSR), C–C chemokine receptor type 5 (CCR5), peroxisome proliferator-activated receptor alpha (PPARα), and interleukin 1beta (IL-1β) play an important role in adiponectin's biological activities and functions. STAT3 has been identified as a common downstream effector of full and globular adiponectin. Both full and globular adiponectin drastically suppress constitutive STAT3 activation in DU145 and HepG2 cells [Miyazaki et al., 2005]. Down-regulation of STAT3 phosphorylation on both tyrosine and serine residues was also observed in HepG2 cells after adiponectin incubation [Sun et al., 2011]. While in primary human hepatocytes and adult mouse cardiac fibroblasts, adiponectin could activate STAT3 [Liao et al., 2009; Wanninger et al., 2009]. The role of adiponectin in diabetes and insulin resistance has been well established [Li et al., 2009]. Plasma adiponectin was suggested to be a marker of INSR dysfunction [Semple et al., 2008]. Furthermore, in INSR transgenic/knockout mice elevated adiponectin level in plasma and decreased PPARα target gene expression in liver were reported [Lin et al., 2007]. In primary human monocytes, adiponectin stimulated release of CCL-2, -3, -4, and -5 while decreased the surface abundance of CCR-2 and -5 is simultaneously [Neumeier

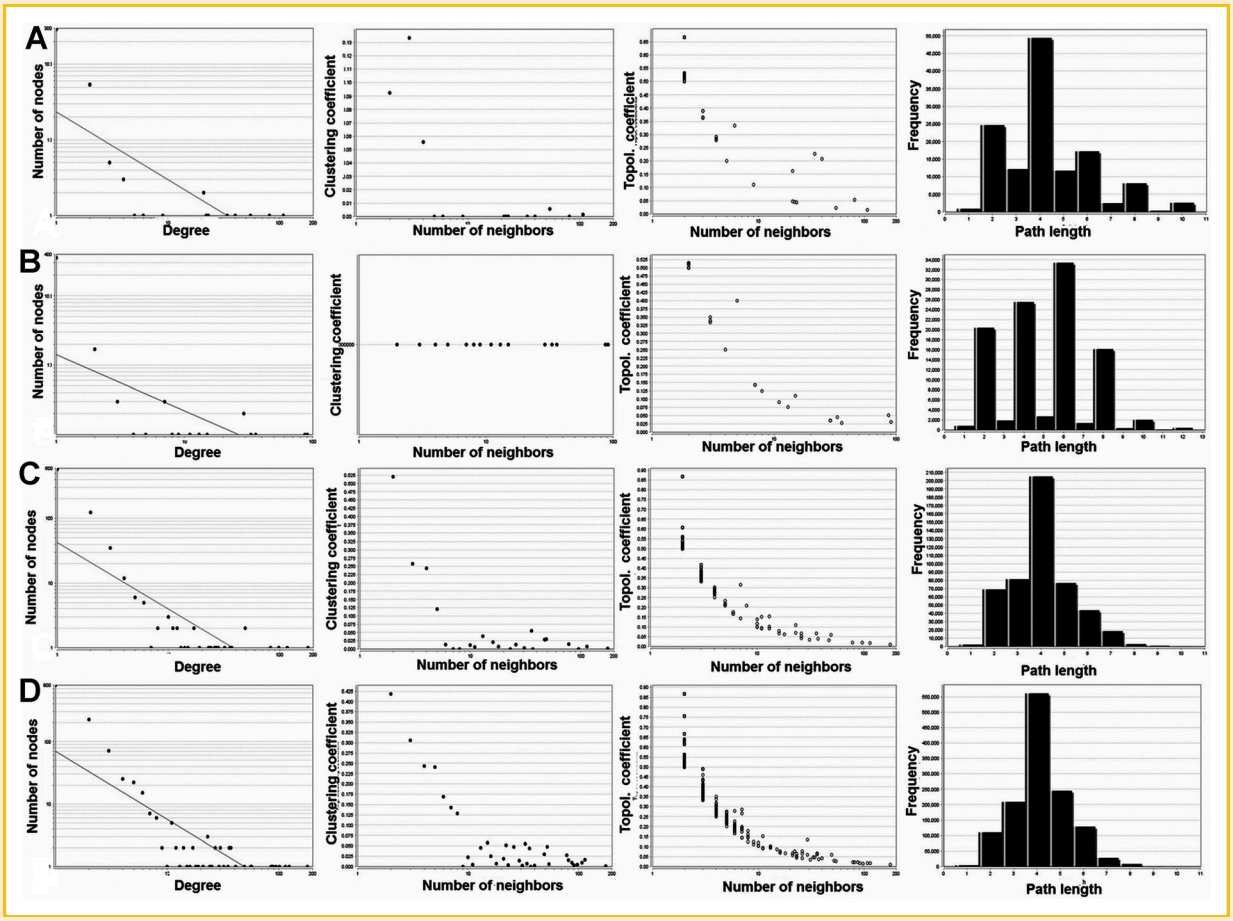

Fig. 3. The topological properties of STN (A), CTTN (B), RTN (C), and TTN (D).

et al., 2011]. In collagen-induced mice arthritis model, adiponectin treatment mitigates the severity of arthritis and decreased expression of IL-1β [Lee et al., 2008]. Therefore, previous studies provide consistent results. CTTN and RTN networks also provide some potential important signaling transduction molecules such as glycogen synthase kinase 3β (GSK3β), toll-like receptor 4 (TLR4), casein kinase 2, alpha 1 polypeptide (CSNK2A1), mitogen-activated protein kinase 3 (MAPK3), etc. Taken together, these results will facilitate the dissection of adiponectin related signaling pathways and will be helpful for the identification of key signaling molecules and drug target candidates.

TABLE I. Topological Properties of Adiponectin Associated Drug Targets Based Networks

Parameter	STN	CTTN	RTN	TTN
Number of nodes	364	388	783	1,207
Number of edges	425	393	1017	1,835
Characteristic path length	4.299	5.052	4.019	4.140
Network diameter	10	12	10	10
Avg. number of neighbors	2.330	2.026	2.557	2.961
Network density	0.006	0.005	0.003	0.002
Network centralization	0.290	0.231	0.222	0.144
Clustering coefficient	0.016	0	0.099	0.111
Network heterogeneity	3.510	3.510	3.688	3.275

Taken together, this study constructed four networks for adiponectin associated drug targets and the topological properties of these networks were analyzed as well, which might be facilitate the dissection of adiponectin related signaling pathways and adiponectin signaling based drug discovery. However, present method also demonstrated several defects. Previous study demonstrated that just like "junk" DNA and spurious DNA binding sites there are nonselected, nonfunctional PPIs in the complicated protein interaction networks. The existence of this "noisy" could help to explain why PPIs determined from large-scale studies often lack functional relationships between interacting proteins [Levy et al., 2009]. Therefore, distinguish of functional and nonfunctional PPIs could be an important step in establishment and analysis of biological protein networks. In this study, all the PPIs were considered as functional ones which might overestimate the role of some biomolecules in adiponectin related signaling transduction pathways. In addition, since user-friendly and publicly accessible web-servers represent the future direction for developing practically more useful models, simulated methods, or predictors [Chou and

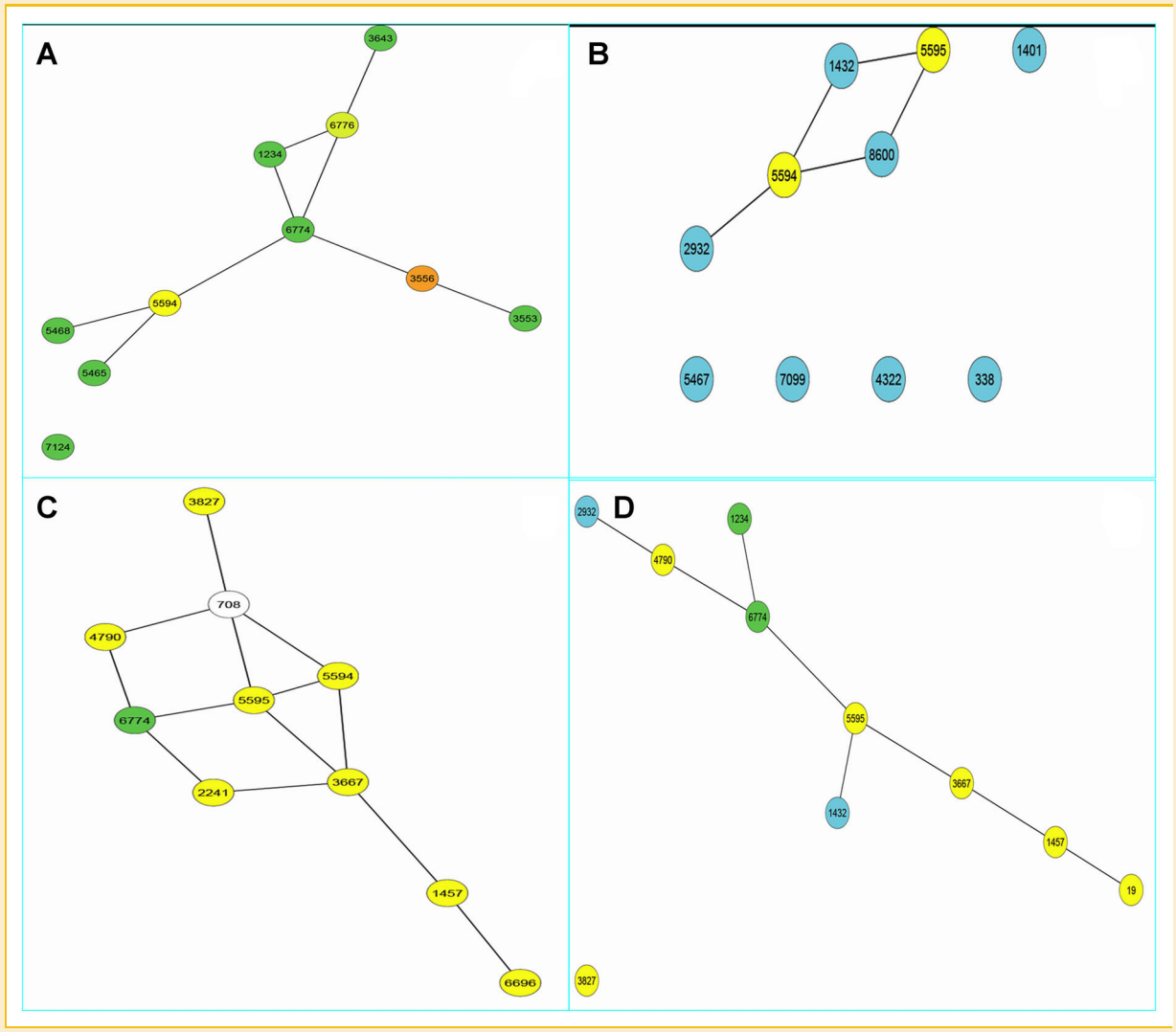

Fig. 4. Hubba analysis adiponectin associated target networks. The top 10 nodes of the adiponectin associated target networks were explored in Hubba. STN (A), CTTN (B), RTN (C), and TTN (D).

TABLE II. The Top Five Ranking Molecules in Adiponectin Associated Drug Target Based Networks

Ranking	STN	CTTN	RTN	TTN
1	6,774 (STAT3)	2,932 (GSK3β)	1,457 (CSNK2A1)	1,457 (CSNK2A1)
2	3,643 (INSR)	7,099 (TLR4)	5,595 (MAPK3)	5,595 (MAPK3)
3	1,234 (CCR5)	86,00 (TNFSF11)	4,790 (NFKB1)	6,774 (STAT3)
4	5,465 (PPARα)	1,432 (MAPK14)	3,667 (IRS1)	2,932 (GSK3β)
5	3,553 (IL-1β)	1,401(CRP)	5,594 (MAPK1)	47,904 (NFKB1)

Shen, 2009], we shall make efforts in our future work to provide a web-server for the method presented in this article.

REFERENCES

Albert R. 2005. Scale-free networks in cell biology. J Cell Sci 118:4947–4957.

Assenov Y, Ramirez F, Schelhorn SE, Lengauer T, Albrecht M. 2008. Computing topological parameters of biological networks. Bioinformatics 24:282–284.

Behre CJ. 2007. Adiponectin, obesity and atherosclerosis. Scand J Clin Lab Invest 67:449–458.

Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD, Palin MF. 2010. Adiponectin action from head to toe. Endocrine 37:11–32.

Buechler C, Wanninger J, Neumeier M. 2010. Adiponectin receptor binding proteins—Recent advances in elucidating adiponectin signalling pathways. FEBS Lett 584:4280–4286.

Chen X, Wang Y. 2011. Adiponectin and breast cancer. Med Oncol 28:1288–1295.

Chen X, Ji ZL, Chen YZ. 2002. TTD: Therapeutic target database. Nucleic Acids Res 30:412–415.

Chen X, Fang Y, Yao L, Chen Y, Xu H. 2007a. Does drug-target have a likeness? Methods Inf Med 46:360–366.

Chen X, Zheng CJ, Han LY, Xie B, Chen YZ. 2007b. Trends in the exploration of therapeutic targets for the treatment of endocrine, metabolic and immune disorders. Endocr Metab Immune Disord Drug Targets 7:225–231.

Chou KC, Cai YD. 2006. Predicting protein–protein interactions from sequences in a hybridization space. J Proteome Res 5:316–322.

Chou KC, Shen HB. 2009. Recent advances in developing web-servers for predicting protein attributes. Nat Sci 1:63–92.

Chou KC, Wu ZC, Xiao X. 2012. iLoc-Hum: Using the accumulation-label scale to predict subcellular locations of human proteins with both single and multiple sites. Mol Biosyst 8:629–641.

Doncheva NT, Assenov Y, Domingues FS, Albrecht M. 2012. Topological analysis and interactive visualization of biological networks and protein structures. Nat Protoc 7:670–685.

Gao P, Wang QP, Chen L, Huang T. 2012. Prediction of human genes' regulatory functions based on protein–protein interaction network. Protein Pept Lett 19:910–916.

Guebre-Egziabher F, Drai J, Fouque D. 2007. Adiponectin and chronic kidney disease. J Ren Nutr 17:9–12.

Han SH, Sakuma I, Shin EK, Koh KK. 2009. Antiatherosclerotic and anti-insulin resistance effects of adiponectin: Basic and clinical studies. Prog Cardiovasc Dis 52:126–140.

Hase T, Tanaka H, Suzuki Y, Nakagawa S, Kitano H. 2009. Structure of protein interaction networks and their implications on drug design. PLoS Comput Biol 5:e1000550.

Heiker JT, Kosel D, Beck-Sickinger AG. 2010. Molecular mechanisms of signal transduction via adiponectin and adiponectin receptors. Biol Chem 391:1005–1018.

Hu L, Huang T, Shi X, Lu WC, Cai YD, Chou KC. 2011a. Predicting functions of proteins in mouse based on weighted protein–protein interaction network and protein hybrid properties. PLoS ONE 6:e14556.

Hu LL, Huang T, Cai YD, Chou KC. 2011b. Prediction of body fluids where proteins are secreted into based on protein interaction network. PLoS ONE 6:e22989.

Hu LL, Feng KY, Cai YD, Chou KC. 2012. Using protein–protein interaction network information to predict the subcellular locations of proteins in budding yeast. Protein Pept Lett 19:644–64451.

Huang T, Chen L, Cai YD, Chou KC. 2011a. Classification and analysis of regulatory pathways using graph property, biochemical and physicochemical property, and functional property. PLoS ONE 6:e25297.

Huang T, Niu S, Xu Z, Huang Y, Kong X, Cai YD, Chou KC. 2011b. Predicting transcriptional activity of multiple site p53 mutants based on hybrid properties. PLoS ONE 6:e22940.

Hui X, Lam KS, Vanhoutte PM, Xu A. 2012. Adiponectin and cardiovascular health: An update. Br J Pharmacol 165:574–590.

Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, Yamaguchi M, Namiki S, Nakayama R, Tabata M, Ogata H, Kubota N, Takamoto I, Hayashi YK, Yamauchi N, Waki H, Fukayama M, Nishino I, Tokuyama K, Ueki K, Oike Y, Ishii S, Hirose K, Shimizu T, Touhara K, Kadowaki T. 2010. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. Nature 464:1313–1319.

Jasmine F, Rahaman R, Dodsworth C, Roy S, Paul R, Raza M, Paul-Brutus R, Kamal M, Ahsan H, Kibriya MG. 2012. A genome-wide study of cytogenetic changes in colorectal cancer using SNP microarrays: Opportunities for future personalized treatment. PLoS ONE 7:e31968.

Kadowaki T, Yamauchi T. 2005. Adiponectin and adiponectin receptors. Endocr Rev 26:439–451.

Kar G, Gursoy A, Keskin O. 2009. Human cancer protein–protein interaction network: A structural perspective. PLoS Comput Biol 5:e1000601.

Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang SH, Kim SE, Lee GY, Lee JW, Jung SA, Chung HY, Jeong S, Kim JB. 2010. Adiponectin represses colon cancer cell proliferation via AdipoR1- and -R2-mediated AMPK activation. Mol Endocrinol 24:1441–1452.

Klipp E, Wade RC, Kummer U. 2010. Biochemical network-based drug-target prediction. Curr Opin Biotechnol 21:511–516.

Kusunoki N, Kitahara K, Kojima F, Tanaka N, Kaneko K, Endo H, Suguro T, Kawai S. 2010. Adiponectin stimulates prostaglandin E(2) production in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 62:1641–1649.

Lee SW, Kim JH, Park MC, Park YB, Lee SK. 2008. Adiponectin mitigates the severity of arthritis in mice with collagen-induced arthritis. Scand J Rheumatol 37:260–268.

Levy ED, Landry CR, Michnick SW. 2009. How perfect can protein interactomes be? Sci Signal 2: pe11.

Li S, Shin HJ, Ding EL, van Dam RM. 2009. Adiponectin levels and risk of type 2 diabetes: A systematic review and meta-analysis. JAMA 302:179–188.

Li BQ, Huang T, Liu L, Cai YD, Chou KC. 2012. Identification of colorectal cancer related genes with mRMR and shortest path in protein–protein interaction network. PLoS ONE 7:e33393.

Liao W, Yu C, Wen J, Jia W, Li G, Ke Y, Zhao S, Campell W. 2009. Adiponectin induces interleukin-6 production and activates STAT3 in adult mouse cardiac fibroblasts. Biol Cell 101:263–272.

Lin HV, Kim JY, Pocai A, Rossetti L, Shapiro L, Scherer PE, Accili D. 2007. Adiponectin resistance exacerbates insulin resistance in insulin receptor transgenic/knockout mice. Diabetes 56:1969–1976.

Lin CY, Chin CH, Wu HH, Chen SH, Ho CW, Ko MT. 2008. Hubba: Hub objects analyzer—A framework of interactome hubs identification for network biology. Nucleic Acids Res 36:W438–W443.

Lin WZ, Fang JA, Xiao X, Chou KC. 2011. iDNA-Prot: Identification of DNA binding proteins using random forest with grey model. PLoS ONE 6:e24756.

Liu ZP, Wang Y, Zhang XS, Chen L. 2012. Network-based analysis of complex diseases. IET Syst Biol 6:22–33.

Miyazaki T, Bub JD, Uzuki M, Iwamoto Y. 2005. Adiponectin activates c-Jun NH2-terminal kinase and inhibits signal transducer and activator of transcription 3. Biochem Biophys Res Commun 333:79–87.

Neumeier M, Bauer S, Bruhl H, Eisinger K, Kopp A, Abke S, Walter R, Schaffler A, Buechler C. 2011. Adiponectin stimulates release of CCL2, -3, -4 and -5 while the surface abundance of CCR2 and -5 is simultaneously reduced in primary human monocytes. Cytokine 56:573–580.

Robinson K, Prins J, Venkatesh B. 2011. Clinical review: Adiponectin biology and its role in inflammation and critical illness. Crit Care 15:221.

Ruffner H, Bauer A, Bouwmeester T. 2007. Human protein–protein interaction networks and the value for drug discovery. Drug Discov Today 12:709–716.

Semple RK, Cochran EK, Soos MA, Burling KA, Savage DB, Gorden P, O'Rahilly S. 2008. Plasma adiponectin as a marker of insulin receptor dysfunction: Clinical utility in severe insulin resistance. Diabetes Care 31:977–979.

Sharan R, Ideker T. 2006. Modeling cellular machinery through biological network comparison. Nat Biotechnol 24:427–433.

Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. 2005. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med 11:1096–1103.

Sun H, Zhang Y, Gao P, Li Q, Sun Y, Zhang J, Xu C. 2011. Adiponectin reduces C-reactive protein expression and downregulates STAT3 phosphorylation induced by IL-6 in HepG2 cells. Mol Cell Biochem 347:183–189.

Wang J, Huo K, Ma L, Tang L, Li D, Huang X, Yuan Y, Li C, Wang W, Guan W, Chen H, Jin C, Wei J, Zhang W, Yang Y, Liu Q, Zhou Y, Zhang C, Wu Z, Xu W, Zhang Y, Liu T, Yu D, Chen L, Zhu D, Zhong X, Kang L, Gan X, Yu X, Ma Q, Yan J, Zhou L, Liu Z, Zhu Y, Zhou T, He F, Yang X. 2011a. Toward an understanding of the protein interaction network of the human liver. Mol Syst Biol 7:536.

Wang P, Xiao X, Chou KC. 2011b. NR-2L: A two-level predictor for identifying nuclear receptor subfamilies based on sequence-derived features. PLoS ONE 6:e23505.

Wanninger J, Neumeier M, Weigert J, Bauer S, Weiss TS, Schaffler A, Krempl C, Bleyl C, Aslanidis C, Scholmerich J, Buechler C. 2009. Adiponectin-stimulated CXCL8 release in primary human hepatocytes is regulated by ERK1/ERK2, p38 MAPK, NF-kappaB, and STAT3 signaling pathways. Am J Physiol Gastrointest Liver Physiol 297:G611–G618.

Wiles AM, Doderer M, Ruan J, Gu TT, Ravi D, Blackman B, Bishop AJ. 2010. Building and analyzing protein interactome networks by cross-species comparisons. BMC Syst Biol 4:36.

Wu ZC, Xiao X, Chou KC. 2011. iLoc-Plant: A multi-label classifier for predicting the subcellular localization of plant proteins with both single and multiple sites. Mol Biosyst 7:3287–3297.

Zhang X, Zhang R, Jiang Y, Sun P, Tang G, Wang X, Lv H, Li X. 2011. The expanded human disease network combining protein–protein interaction information. Eur J Hum Genet 19:783–788.

Zhu M, Gao L, Li X, Liu Z, Xu C, Yan Y, Walker E, Jiang W, Su B, Chen X, Lin H. 2009. The analysis of the drug-targets based on the topological properties in the human protein–protein interaction network. J Drug Target 17:524–532.

Zhu F, Han B, Kumar P, Liu X, Ma X, Wei X, Huang L, Guo Y, Han L, Zheng C, Chen Y. 2010. Update of TTD: Therapeutic target database. Nucleic Acids Res 38:D787–D791.

Zhu F, Shi Z, Qin C, Tao L, Liu X, Xu F, Zhang L, Song Y, Zhang J, Han B, Zhang P, Chen Y. 2012. Therapeutic target database update 2012: A resource for facilitating target-oriented drug discovery. Nucleic Acids Res 40:D1128–D1136.