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Functional modules and bottlenecks in human metabolic network core

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The objective of this paper was to study human metabolic network core by structural and functional analysis. Firstly, we edited the human metabolic network core derived from a high-quality human metabolic network model and studied its general global structural properties (degree distribution, average path length, etc.). The human metabolic network core is a "scale-free" and "small-world" network. Then, we studied modules in human metabolic network core based on simulated annealing algorithm. The functional significance of these modules for metabolism was investigated by comparing them to KEGG metabolic pathways. Finally, we studied central metabolites in human metabolic network core by multi-centrality measures and discussed their biological implications and pharmacological insight.

Key words: centrality, biological network, modularity, scale-free, small-world.

INTRODUCTION

Remarkable advances in whole genome sequencing and high-throughput experimental technologies enable the scientific community to obtain the full knowledge of interactions among cellular components (Reed *et al*., 2006). These interactions were generally represented by networks (Aittokallio & Schwikowski, 2006), in which the nodes (e.g. metabolites) are linked by arcs or edges (metabolic reactions accordingly). Because detailed kinetic parameters are hardly available, lots of recent studies have focused on structural and functional analysis of these networks. The results so far suggested that these structural-oriented methods had been invaluable in understanding cellular organizational principles and proposing new hypotheses (Aittokallio & Schwikowski, 2006; Palsson, 2006; Chaouiya, 2007; Ding & Li, 2009; Ding *et al*., 2009). Since Ma and Zeng proposed the "bow tie" structure of metabolic networks, it is increasingly recognized that this structural property is functionally meaningful for metabolism, disease and the design principle of biological robustness (Ma & Zeng, 2003a). Generally speaking, a network with the "bow tie" structure could be decomposed into four parts: Giant Strong Component (GSC), Substrate Subset (S), Product Subset (P) and Isolated Subset (IS). The GSC is the biggest strongly connected component of a metabolic network, it determines the structure of the entire network at a certain extent, and thus is considered as the metabolic network core (Zhao *et al*., 2007). In the late 1990s, Watts & Strogatz investigated the average path length of real networks and introduced the so-called "small-world" networks, i.e., natural complex networks with very small average path lengths (Watts & Strogatz, 1998). Later, "scale-free" network theory was introduced (Barabási & Oltvai, 2004) for natural complex networks with power-law node degree distributions (i.e., the degree distribution P(k) of the nodes follows the function $P(k) = ak^{-r}$, $a > 0$, $r > 0$). These two general network properties (and their slight but exquisite variants) have lately attracted much attention. Recent experimental

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and theoretical studies have shown that most biological networks (such as metabolic networks, protein-protein interaction networks, transcriptional regulatory networks, signal transduction networks, etc.) displayed "scale-free" and "small-world" characters (Ma & Zeng, 2003a, b; Barabási & Oltvai, 2004; Albert, 2005; Aittokallio & Schwikowski, 2006).

In this article, we firstly edited the human metabolic network core from a recently reconstructed high-quality human metabolic network. The resulted network contains 256 vertices and 648 arcs. We then analyzed its global structural properties. Finally, the structure of the metabolic network core is explained and discussed based on modularity and centrality analysis, focusing on their biological and pharmacological significance.

We used modularity analysis because 1) the metabolic networks are often so large that combinatorial explosion of pathways makes it difficult to apply traditional pathway analysis methods to the whole networks, and 2) we need to identify functional modules to discover functional information involved in metabolic networks.

Since it has been proposed, modularity analysis is specifically useful, among other structural analysis methods, for the structural and functional analysis of metabolic networks. Modularity analysis is also used for the analysis of other complex networks, such as social networks, Internet, World Wide Web, etc. (Guimerà & Amaral, 2005; Gulbahce & Lehmann, 2008).

Centrality analysis is another important method we engaged, which is used to rank elements of a network and hence it helps to determine which individual nodes of a network are more important than others (Junker *et al*., 2006). For example, Fell & Wagner (2000) showed that the most central metabolites in metabolic networks are evolutionarily conserved, while Jeong *et al.* (2001) showed that central proteins in yeast protein-protein interaction networks are often indispensable. However, it is clear that one specific centrality measure is not sufficient when used alone, thus several centrality measures have to be considered for biological network analysis.

MATERIALS AND METHODS

Human Metabolic Network Core

High-quality human metabolic networks have attracted much attention recently, as they would be valuable for understanding the relationship between human metabolism and diseases (Goh *et al*., 2007; Lee *et al*., 2008; Ma & Goryanin, 2008). Currently, we have two acquirable high-quality human metabolic network models available: The Edinburgh human metabolic network (Ma *et al*., 2007) and *H. sapiens* Recon 1 (Duarte *et al*., 2007). To reflect biologically meaningful transformations, we used the Edinburgh human metabolic network model (Ma *et al*., 2007) in this work. All reactions in Ma *et al*. (2007) are edited based on the following principles: 1) some obvious inconsistencies (e.g., the inconsistencies in compound names, the mistakes in reaction equations, etc.) were corrected, 2) the reversibility of every reaction was confirmed, 3) some small molecules and some meta-

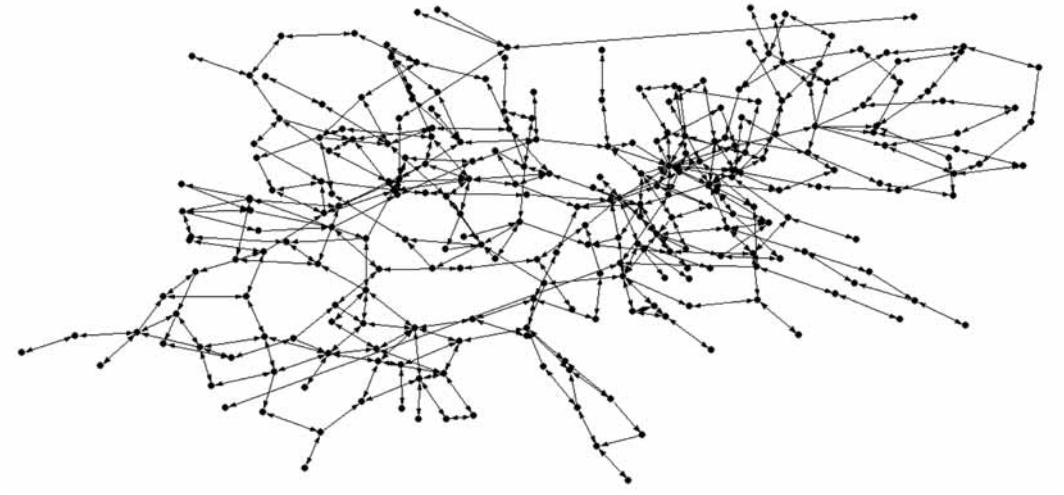


FIG. 1. Human metabolic network core topology structure, the vertices correspond to metabolites and the arcs correspond to reactions. The picture was drawn using the Pajek program (Batagelj & Mrvar, 1998).

bolites which are typical for transferring electrons (ATP, ADP, NADH, H_2O, etc.) were excluded. Then, all of the metabolic reactions involved in the model are represented by the so-called metabolite graph, i.e. the vertices are metabolites and the arcs are reactions. For example, after excluding ATP and ADP, from the reaction ATP + D-glucose = ADP + D-glucose 6-phosphate only the vertices D-glucose and D-glucose 6-phosphate were left, connected with the arc D-glucose → D-glucose 6-phosphate. For encoding the reactions and the compound names we used the codes of Ma's database (Ma *et al*., 2007). Most, but not all, reactions in Ma follow the codes provided in the KEGG LIGAND database (http://www.genome.jp/ligand/). For instance, Acetyl-CoA is represented by the code C00024. We then extracted the human metabolic network core. It contains 256 vertices and 648 arcs. The topology of the human metabolic network core is shown in Figure 1.

Modularity Measures

The definition of functional modules in biological networks is similar in principle to the definition of communities in social networks. A functional module is a set of nodes with dense node-node links within the module but with sparser links between different modules (Newman, 2006). An example network, which could be decomposed to three modules, is depicted in Figure 2.

An important parameter related to the detection of modules is modularity. For any presumptive partition of the network nodes, into modules, the partition modularity M is defined as (Guimerà *et al*., 2004):

$$M \equiv \sum_{s=1}^{r} \left[\frac{l_s}{L} - \left(\frac{d_s}{2L} \right)^2 \right] \qquad (1)$$

where r is the number of modules, l_s is the number of links between nodes in module s, d_s is the sum of the degrees of the nodes in module s, and L is the total number of links in the entire network. For the identification of the best partition of the nodes into modules, we engaged simulated annealing algorithm. Here, simulated annealing is a stochastic optimization technique that tries to find the optimal partition of nodes into modules by maximizing the network modularity (Guimerà & Amaral, 2005), using a cost function of the form C = –M, where M is the modularity defined in equation (1). Simulated annealing could find 'low cost' configurations without getting trapped in 'high cost' local minima.

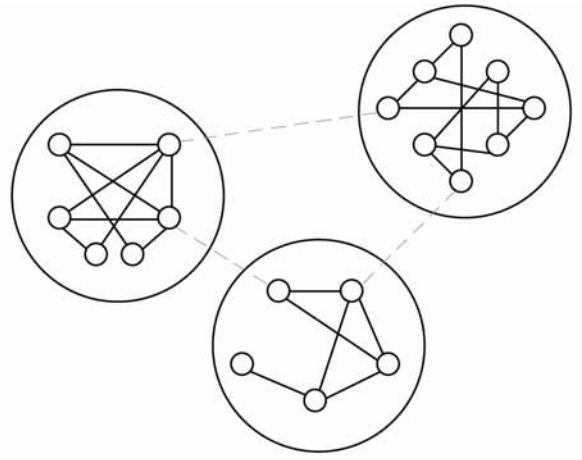


FIG. 2. A paradigm network with three modules.

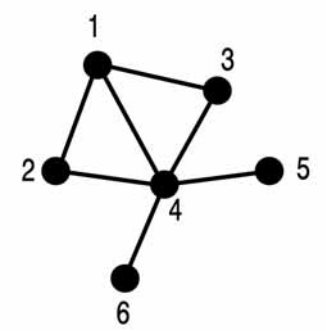
Starting from an initial configuration, the method produces some random updates at each simulation step by translocation of a number of nodes from one module to another. At each step some of the random updates are accepted with probability:

$$p = \begin{cases} 1 & \text{if } C_2 \le C_1 \\ \exp\left(-\dfrac{C_2 - C_1}{T}\right) & \text{if } C_2 \ge C_1 \end{cases} \qquad (2)$$

where C_2 and C_1 are the cost after the update and before the update respectively, while T is the computational temperature. Generally, when T is high, the system can explore high cost, and when T is low, the system only explores low cost. For finding the low cost, T is slowly decreasing from a high initial value. Specifically, at each temperature T there would be $n_i = fS^2$ individual node movements and $n_c = fS$ collective node movements from one module to another, where S is the number of nodes in the network, and f is iteration factor with the recommended range of 0.1 to 1. At each simulation step, the system would be cooled down to $T_1 = cT$, where c is the cooling factor.

Centrality Measures

Centrality measure methods are used to rank elements of a network and hence to determine which individual nodes of a network are more important than others. Generally speaking, centrality is a function that assigns a numerical value C(v) to each vertex of a network, and there are many different measures for computing such a centrality (Junker *et al*., 2006). Degree centrality calculates the number of connections of each vertex in the network, and thus is used to



Rank	Vertices	Numerical Value
1	4	5
2	1	3
3	2	2
4	3	2
5	5	1
6	6	1

FIG. 3. The degree centrality measure in a paradigm network (adopted from exercise in Koschützki, 2008). Degree centrality measure ranks vertices in a network by calculating the number of connections of each vertex. E.g., for vertex 4, there are 5 links, so the numerical value for it is 5.

TABLE 1. Definitions for the centrality measures used in this study. $d(v)$ denotes the degree of the vertex v, $dist(v, w)$ denotes the length of a shortest path between the vertices v and w, $\sigma_{st}(v)$ denotes the number of shortest path from s to t that use the vertex v, $\delta_{st}(v) = \sigma_{st}(v)/\sigma_{st}$, where σ_{st} denotes the number of shortest paths from s to t, A denotes the adjacency matrix of the graph and $\bar{1}$ the unit vector

Name	**Definition**
Degree	$C_{deg}(v) = d(v)$
Eccentricity	$C_{ecc}(v) = 1/(\max_{w\in V} dist(v, w))$
Closeness	$C_{clo}(v) = 1/(\sum_{w\in V} dist(v, w))$
Radiality	$C_{rad}(v) = \sum T_{w\in V}(\Delta_G + 1\text{-}dist(v,w))/(n\text{-}1)$
Centroid Value	$C_{cen}(v) = \min_{w\in V\setminus\{v\}}\{f(v,w)\}$
Shortest Path Betweenness	$C_{spb}(v) = \sum_{S\neq v\in V}\sum_{t\neq v\in V}\delta_{st}(v)$
Katz Status	$C_{katz} = \sum a^k (A^T)^k \bar{1}$
Eigenvector	$\lambda C_{eiv} = AC_{eiv}$
PageRank	$C_{pr} = dPC_{pr} + (1\text{-}d)\bar{1}$
HITS-Hubs	$C_{hubs} = AC_{auths}$

identify the hub metabolites (Fig. 3). Betweenness centrality calculates the number of shortest pathways going through the vertices, while closeness centrality considers the vertices in the core and periphery part of the network. The centrality measures used in this study are according to Junker *et al*. (2006) and are summarized in Table 1.

RESULTS AND DISCUSSION

General Network Property of Human Metabolic Network Core

Firstly, we checked whether the human metabolic network core could be characterized as a "scale-free", "small-world" network. We firstly investigated the in-degree (the number of directed links that point to the node) distributions, out-degree (the number of directed links that start at the node) distributions and total-degree (the number of total links) distributions of human metabolic network core. The results (Figs 4, 5 and 6) reaffirm that all of these degree distributions (log-log) approximately follow power law, and suggest that the network is "scale-free". We then computed the average path length and the network diameter, which is defined as the path length of the longest pathway among all of the shortest pathways. The average path length is 10.54 steps and network diameter is 46 steps for the human metabolic network core, which is similar to other eukaryotes studied by Ma & Zeng (2003b) (see Table 2). This result indi-

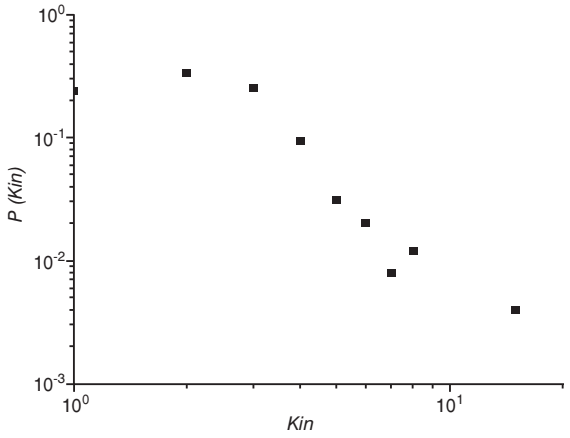


FIG. 4. Log-log plot of the in-degree distributions for human metabolic network core.

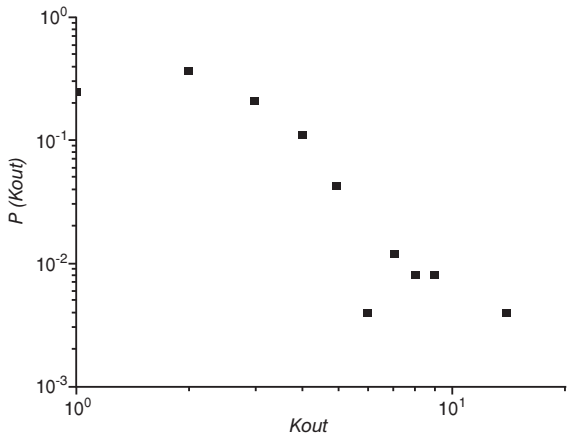


FIG. 5. Log-log plot of the out-degree distributions for human metabolic network core.

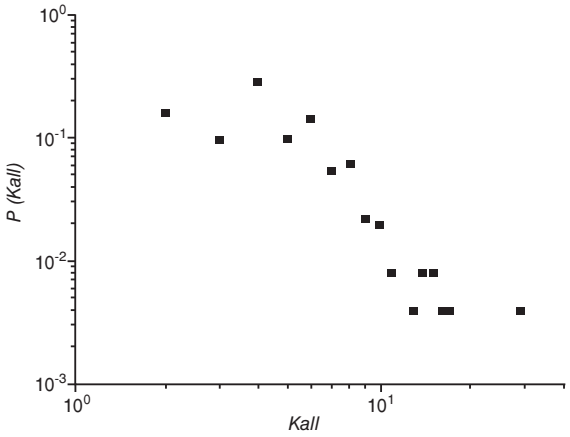


FIG. 6. Log-log plot of the total degree distributions for human metabolic network core.

TABLE 2. Average path length (AL) and diameter (D) of some eukaryotes

Organisms	**Abbreviation**	**AL**	**D**
Arabidopsis thaliana	ath	7.33	21
Caenorhabditis elegans	cel	10.87	49
Drosophila melanogaster	dme	9.41	24
Homo sapiens	hsa	11.33	46
Mus musculus	mmu	7.34	23
Rattus norvegicus	rno	10.99	38
Saccharomyces cerevisiae	sce	9.71	31

TABLE 3. Decomposed results of human metabolic network core based on simulated annealing algorithm

Module	Nodes	Total links	Within links	Between links
1	28	55	38	17
2	15	27	20	7
3	37	47	44	3
4	17	27	22	5
5	10	15	12	3
6	46	77	63	14
7	31	53	43	10
8	29	42	38	4
9	12	18	12	6
10	31	54	45	9

Modularity = 0.775701

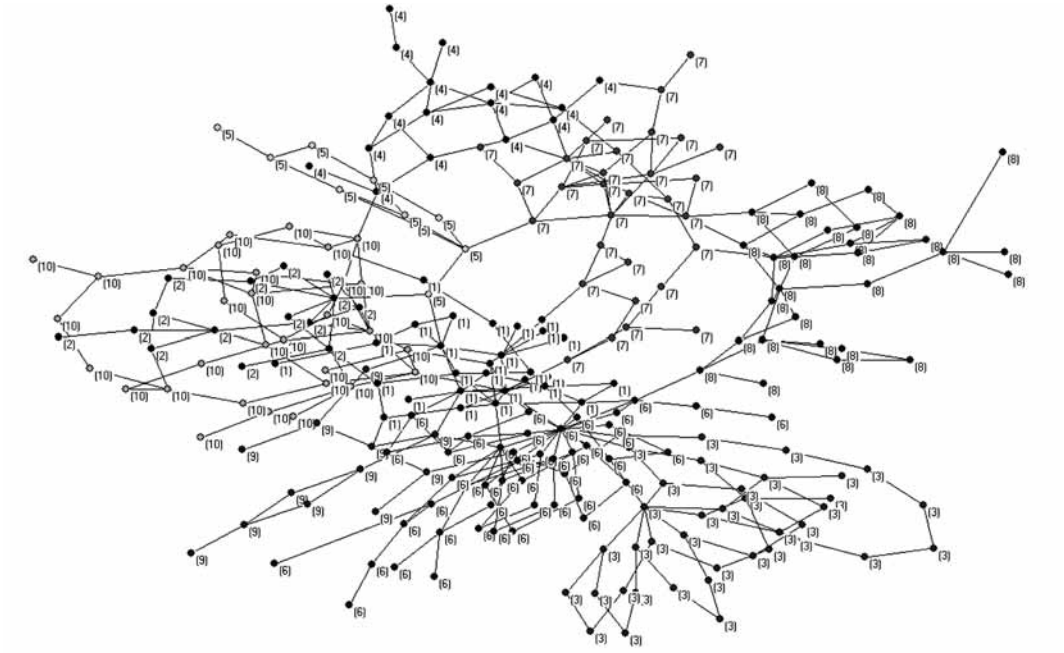


FIG. 7. Modules in human metabolic network core. Each module (indicated by different colors and numbers) is signed by its module No. (the same numbers are also used in Tables 3 and 4). The picture was drawn using the Pajek program (Batagelj & Mrvar, 1998).

cates that the human metabolic network core is a "small-world" network.

Modules of Human Metabolic Network Core

The best partition of the human metabolic network core into modules (Fig. 7) is one with 10 modules. For each module, we give the number of metabolites (i.e., the nodes), total links (i.e., all links in the whole network), within-module links (i.e., links within the partition) and between-module links (i.e., links between the partitions). The modularity of the partition is 0.775701. The decomposed result is also reaffirmed by KEGG metabolic pathways, i.e. most modules are mainly corresponding to one or two KEGG pathways (Table 4). For instance, 19 out of 20 within links in module 2 are corresponding to purine metabolism and 41 out of 44 within links in module 3 are corresponding to fatty acid biosynthesis. Of the 45 within links in module 10, 28 correspond to pyrimidine and 12 to purine metabolism. Thus, it is clear that the

TABLE 4. The decomposed results of human metabolic network core is reaffirmed by compared to KEGG metabolic pathways

——— represents that the corresponding module includes several pathways and it is difficult to assign it one or two simple pathways

Module	**Pathways in KEGG**
1	———
2	Purine metabolism
3	Fatty acid biosynthesis
4	Galactose metabolism, Glycolysis/Gluconeogenesis
5	Aminosugars metabolism
6	Fatty acid elongation in mitochondria
7	PPP, Glycolysis/Gluconeogenesis, Fructose and mannose metabolism
8	Glycerolipid metabolism, Glycerophospholipid metabolism
9	———
10	Pyrimidine metabolism, Purine metabolism

modules detected by the simulated annealing algorithm are of functional significance for metabolism. The modular structure of the network that encapsulates simple functions in each module is a basic mechanism than enable biological robustness (Kitano, 2004; Stelling *et al*., 2004; Ding *et al*., 2008). The reason is that any damage located in one module is prevented from spreading throughout the entire network. That is, the modular structure reduces the risk of a catastrophic failure.

Centers of Human Metabolic Network Core

The multi-centrality measures of human metabolic network core were computed. The central metabolites were different according to different centrality measures. So we first ranked the top 20 central metabolites for every centrality measure (Table 5). The ranks depended on the centrality measure used since different measures focus on different aspects of centrality. To select the 10 top central metabolites we only considered those included in the top 20 list of at

TABLE 5. The top 20 central metabolites corresponding to different centrality measures. Degree, V_{deg}; Eccentricity, V_{ecc}; Closeness, V_{clo}; Radiality, V_{rad}; Centroid Value, V_{cen}; Shortest Path Betweenness, V_{spb}; Katz Status, V_{katz}; Eigenvector, V_{eig}; PageRank, V_{pr}; VHITS-Hubs, V_{hubs}

Rank	V_{deg}	V_{ecc}	V_{clo}	V_{rad}	V_{cen}	V_{spb}	V_{katz}	V_{eig}	V_{pr}	V_{hubs}
1	24	65	22	22	22	24	24	24	24	10
2	10	3232	65	65	25	10	10	10	10	22
3	46	36	26	26	64	22	46	22	3968	158
4	5345	22	41	41	26	118	5345	158	330	24
5	22	64	25	25	111	36	118	33	5345	5265
6	118	168	64	64	93	197	26	26	118	5263
7	25	116	36	36	5378	26	36	91	4618	5269
8	26	577	168	168	41	236	91	5269	361	5267
9	36	258	91	91	5345	8	25	5263	6326	5261
10	3968	197	10	10	49	631	22	5267	631	5259
11	91	1005	49	49	668	74	8	5261	4317	33
12	41	10	149	149	36	46	5382	5259	117	222
13	5382	26	1005	1005	577	5259	3968	5265	91	579
14	4317	41	311	311	24	5258	33	36	197	332
15	117	186	186	186	118	25	231	579	242	1136
16	1209	256	256	256	10	91	117	311	46	5993
17	144	25	158	158	231	5272	279	136	106	26
18	8	49	258	258	279	111	144	5274	877	25
19	361	29	5379	5379	258	33	5378	5270	3372	36
20	352	158	2630	2630	168	154	85	1832	5747	49

Note: The metabolite names for each ID used in the Table: 8, ADP; 10, CoA; 22, Pyruvate; 24, Acetyl-CoA; 25, L-Glutamate; 26, 2-Oxoglutarate; 29, UDPglucose; 33, Acetate; 36, Oxaloacetate; 41, L-Alanine; 46, RNA; 49, L-Aspartate; 64, L-Glutamine; 65, L-Serine; 74, Phosphoenolpyruvate; 85, D-Fructose 6-phosphate; 91, Succinyl-CoA; 93, sn-Glycerol 3-phosphate; 106, Uracil; 111, Glycerone phosphate; 116, Glycerol; 117, D-Ribose 5-phosphate; 118, (2R)-2-Hydroxy-3-(phosphonooxy)-propanal; 136, Butanoyl-CoA; 144, GMP; 149, (S)-Malate; 154, Palmitoyl-CoA; 158, Citrate; 168, Hydroxypyruvate; 186, (S)-Lactate; 197, 3-Phospho-D-glycerate; 222, 3-Oxopropanoate; 231, D-Xylulose 5-phosphate; 236, 3-Phospho-D-glyceroyl phosphate; 242, Guanine; 256, (R)-Lactate; 258, D-Glycerate; 279, D-Erythrose 4-phosphate; 311, Isocitrate; 330, Deoxyguanosine; 332, Acetoacetyl-CoA; 352, D-Glucosamine 6-phosphate; 361, dGDP; 577, D-Glyceraldehyde; 579, Dihydrolipoamide; 631, 2-Phospho-D-glycerate; 668, alpha-D-Glucose 6-phosphate; 877, Crotonoyl-CoA; 1005, O-Phospho-L-serine; 1136, S-Acetyldihydrolipoamide 1209, Malonyl-[acyl-carrier protein]; 1832, Lauroyl-CoA; 2630, 2-Hydroxyglutarate; 3232, 3-Phosphonooxypyruvate; 3372, Acylglycerone phosphate; 3968, 1-Alkyl-sn-glycero-3-phosphate; 4317, 1-Alkyl-sn-glycerol-3-phosphocholine; 4618, (3R)-3-Hydroxybutanoyl-[acyl-carrier protein]; 5258, (S)-3-Hydroxyhexadecanoyl-CoA; 5259, 3-Oxopalmitoyl-CoA; 5261, 3-Oxotetradecanoyl-CoA; 5263, 3-Oxododecanoyl-CoA; 5265, 3-Oxodecanoyl-CoA; 5267, 3-Oxooctanoyl-CoA; 5269, 3-Oxohexanoyl-CoA; 5270, Hexanoyl-CoA; 5272, trans-Hexadec-2-enoyl-CoA; 5274, Decanoyl-CoA; 5345, beta-D-Fructose 6-phosphate; 5378, beta-D-Fructose 1,6-bisphosphate; 5379, Oxalosuccinate; 5382, Sedoheptulose 7-phosphate; 5747, (R)-3-Hydroxyhexanoyl-[acp]; 5993, Acetyl adenylate; 6326, (2S)-2-{[1-(R)-Carboxyethyl]amino}pentanoate

TABLE 6. The top 10 central metabolites ranked by the number of centrality measures in which the metabolite is a center metabolite

Rank	Vertex	Metabolite name	Abbreviation	Number
1	10	CoA	CoA	10
2	22	Pyruvate	PYR	9
3	26	2-Oxoglutarate	AKG	9
4	36	Oxaloacetate	OAA	9
5	25	L-Glutamate	GLU	8
6	24	Acetyl-CoA	AcCoA	7
7	91	Succinyl-CoA	SuCoA	7
8	41	L-Alanine	ALA	5
9	49	L-Aspartate	ASP	5
10	118	(2R)-2-Hydroxy-3-(phosphonooxy)-propanal	2HPP	5

least one centrality measure. The metabolites in this latter set were eventually ranked according to the number of different top 20 lists they were included and the top ten among them are given in Table 6. Among these top 10 central metabolites, CoA is an ubiquitous molecule and PYR is an important intermediate in the glycolysis pathway. AKG is the metabolite linking TCA cycle with reductive carboxylate cycle (CO_2 fixation) and nitrogen metabolism. OAA links pyruvate metabolism and TCA cycle. AcCoA and SuCoA link glycolysis pathway with citric acid cycle and fatty acid synthesis pathway. 2HPP is the metabolite linking glycolysis pathway, pentose phosphate pathway and carbon fixation. GLU, ALA and ASP are three important amino acids. They are directly produced in TCA cycle and could be converted to many other useful amino acids. Furthermore, from the therapeutic viewpoint, these metabolites are all good drug targets and help in therapy design, because they are involved in many disease-related metabolic reactions. For instance, the top central metabolite, CoA, participates in 15 disease-related reactions: R00234 (Acetyl-CoA + Peptide <=> CoA + Nalpha-Acetylpeptide), R00351 (Citrate + CoA <=> Acetyl-CoA + H_2O + Oxaloacetate), R00352 (ATP + Citrate + CoA <=> ADP + Orthophosphate + Acetyl-CoA + Oxaloacetate), R00395 (Acyl-CoA + Glycine <=> CoA + N-Acylglycine), R01177 (Acetyl-CoA + Butanoyl-CoA <=> CoA + 3-Oxohexanoyl-CoA), R02387 (Acetyl-CoA + Aniline <=> CoA + N-Acetylarylamine), R03552 (Acetyl-CoA + Histone <=> CoA + Acetylhistone), R03778 (Octanoyl-CoA + Acetyl-CoA <=> CoA + 3-Oxodecanoyl-CoA), R03779 (Octanoyl-CoA + L-Carnitine <=> CoA + L-Octanoylcarnitine), R03858 (Lauroyl-CoA + Acetyl-CoA <=> CoA + 3-Oxotetradecanoyl-CoA), R03991 (Tetradecanoyl-CoA + Acetyl-CoA <=> CoA + 3-Oxopalmitoyl-CoA), R03992 (Tetradecanoyl-CoA + Glycylpeptide <=> CoA + N-Tetradecanoylglycylpeptide), R04742 (Decanoyl-CoA + Acetyl-CoA <=> CoA + 3-Oxododecanoyl-CoA), R04747 (Hexanoyl-CoA + Acetyl-CoA <=> CoA + 3-Oxooctanoyl-CoA) and RE0361 (CoA + "a"-ketoglutarate + NAD^+ <=> CO_2 + NADH + succinyl-CoA).

In conclusion, with the accumulation of knowledge in 'omics' and systems biology, high-quality metabolic networks are now available for structural and functional analysis (Reed *et al*., 2006). Since they were published (Duarte *et al*., 2007; Ma *et al*., 2007), high-quality human metabolic networks have attracted much attention in recent years. It is suggested that these studies could greatly help for understanding human metabolism, diseases and for proposing new hypotheses (Goh *et al*., 2007; Lee *et al*., 2008; Ma & Goryanin, 2008).

This study provides an attempt to explore the fundamental organizational principles that underlie human metabolic network core. Our study has been initiated by extracting human metabolic network core from a high-quality human metabolic network. The obtained metabolic network core is represented by a metabolite graph. We analyzed its general global structural properties and validated its "scale-free" and "small-world" characters. Finally, the structure of the metabolic network core is explained and discussed based on modularity and centrality analysis, with their biological and pharmacological significance.

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The human metabolic network core model and supplementary material will be available upon request.

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