Article

Analysis on degree distribution of tumor signaling networks

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Abstract
Tumorigenesis is a multi-factorial and multi-step process, among which the changes in cell signaling pathways play a key role. Up till now there are fewer studies on network structure of tumor signaling pathways. In present study the degree distribution was analyzed based on thirty kinds of tumor signaling networks, including VEGF-pathway, JNK-pathway, p53-signaling, etc. The results showed that almost all of them were scale-free complex networks. Key metabolites in some tumor networks were also described.

Keywords tumor; cancer; signaling pathway; network; degree distribution.

1 Introduction

Tumorigenesis is a multi-factorial and multi-step process. Among them, the changes in cell signaling pathways play a key role. Complex signaling pathways in a human body cell include a large number of ligands, receptors, signaling proteins, and other links, which result in a complex network. Metabolism of tumor signaling is also true. Complex signaling pathways constitute different networks and thus affect the metabolic processes of the tumor.

Tumor signaling pathways are mainly divided into six categories: JAK-STAT signaling pathway, p53 signaling pathway, NF-κB signaling pathway, Ras, PI3K and mTOR signaling pathway, Wnt NF-κB signaling pathway and BMP signaling pathway. There are dozens of ligands, receptors and signaling proteins associating with the six signaling pathways, and each of them has its own complex metabolic signaling pathways. All of them shape a complex and directed network, similar to the various networks reported (Ibrahim et al., 2011; Goemann et al., 2011; Kuang and Zhang, 2011; Martínez-Antonio, 2011; Paris and Bazzoni, 2011; Rodriguez and Infante, 2011; Tacutu et al., 2011; Zhang, 2011, 2012c)

JAK-STAT signaling pathway is primarily made of receptor tyrosine kinases, tyrosine kinases JAK and transcription factor STAT that involve in cell proliferation, differentiation, apoptosis, immune regulation and other important biological processes (Marrer, 2005).

p53 signaling pathway is a signaling metabolic process based on the gene p53 which has the closest relationship with cancer. p53 gene is regulated by a variety of signaling factors (Ho et al., 2006).

In the NF-κB signaling pathway, NF-κB (Nuclear Factor-kappa B) will specifically bind to the enhancer B sequence GGGACTTTCC of kappa light-chain gene of immunoglobulin, and promote the expression of κ light-chain gene, thus affect the metabolism of tumor.

For Ras, PI3K and mTOR signaling way, the key regulatory factors in the Ras and PI3K signaling

pathway undergone significant mutations (Kolch, 2002), which affect the metabolism of the downstream regulation molecule mTOR and lead to disorders of cell growth and the generation of tumor cells (Stauffer et al., 2005).

Wnt metabolism has a crucial role in early development and organ formation of animal embryos, and tissue regeneration and other physiological processes. Mutations of key proteins in the signaling pathway will lead to abnormal activation of signaling and likely induce the occurrence of cancer (Katoh, 2005).

BMP (Bone Morphogenetic Protein) is an important member in the superfamily of TGF-β (Transforming Growth Factor-β). It controls many biological processes, such as tumorigenesis, by regulating the activity of a series of downstream genes (Moustakas et al., 2002).

So far, most studies on tumorigenesis have focused on single metabolic process, mutation induced signaling abnormality and tumorigenesis, and key ligands, receptors, signaling proteins in cancer signaling pathways. However, there were fewer studies on network structures of tumor signaling pathways (Zeitoun et al., 2012).

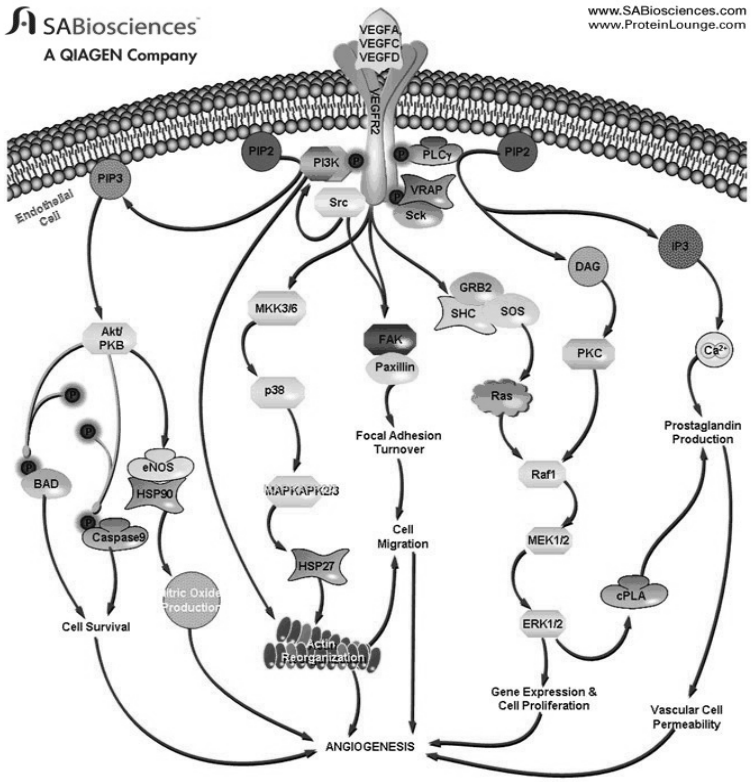

Fig. 1 VEGF-pathway (Source: www.sabiosciences.com)

The most important aspect for network structure is the degree distribution of network (Butts, 2009). Degree distribution depicts the extent of complexity of a network. In random networks, the degree distribution is binomial distribution and its limit is the Poisson distribution. In a random network, most nodes have the same or similar number of connections. In complex networks, the degree distribution is typically a power law distribution. These networks are scale-free networks (Barabasi and Albert, 1999; Barabasi, 2009). A property of the scale-free network is that the structure and the evolution of network are inseparable. Scale-free networks

constantly change because of the arrival of nodes and links (Barabasi and Albert, 1999). In general, the degree of a network can be described with various distribution models, like binomial distribution, Poisson distribution, exponential distribution, power law distribution, etc (Zhang and Zhan, 2011; Zhang, 2012b).

In present study, network structure, including network size, degree distribution (Dunne et al., 2002) and network type, of 30 tumor signaling networks was analyzed using network type detection algorithm in order to provide a deep insight on tumorigenesis and tumor treatment.

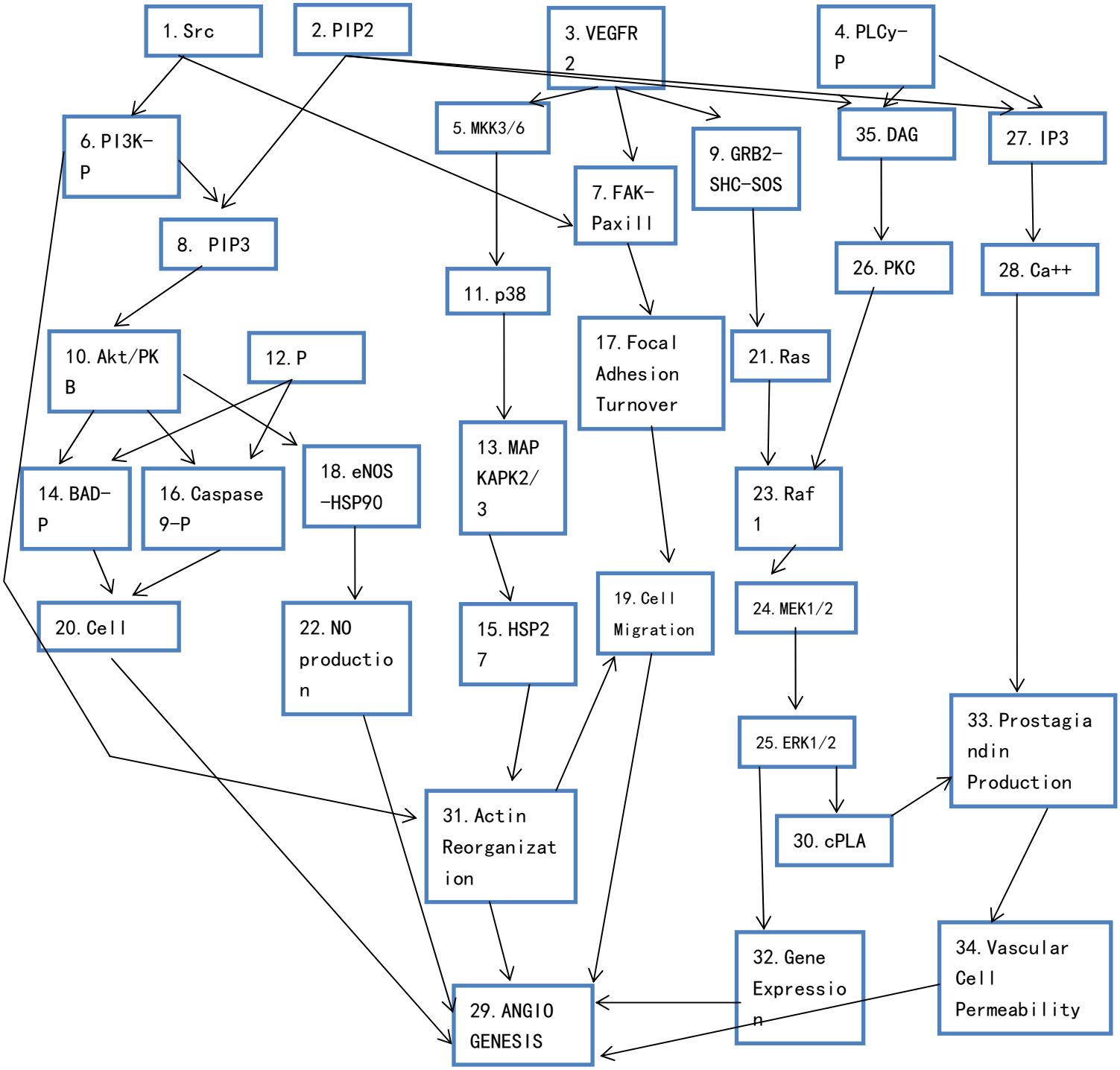

Fig. 2 The graph for VEGF-pathway

2 Material and Methods

2.1 Data sources

Above six signaling pathways are closely related to the signaling pathways of 30 kinds of important metabolites/steps. The later were collated and interpreted to form a new analytical database. All image information for signaling networks were downloaded from SABiosciences (http://www.sabiosciences.com/pathwaycentral.php) (Pathway Central, 2012) and Abcam (http://www.abcam.com/) (Abcam, 2012). For example, the image of VEGF-pathway is indicated in Fig. 1.

In Fig.1, all VEGF-pathway related metabolites/steps, metabolic paths and directions were clearly given. The image in Fig. 1 may be further transformed into a clearer graph with nodes and directed connections, as indicated in Fig. 2. Each metabolite/step (node) in the graph was given an ID number. The arrows represented between-metabolite/step relationships (However, a clear graph may also be drawn by using the programs of Arnold et al. (2012) and Zhang (2012a)).

In present study, the graphs are undirected graphs, i.e., all connections are undirected connections (they are represented by 1). The graph in Fig. 2 was transformed into the data used in netType program (Zhang, 2012b; Zhang and Zhan, 2011), as indicated in Table 1.

Table 1 The data of VEGF-pathway used in netType program

ID for from metabolite/step	ID for to metabolite/step	Relation-ship	ID for from metabolite/step	ID for to metabolite/step	Relation-ship
1	6	1	14	20	1
1	7	1	15	31	1
2	8	1	16	20	1
2	27	1	17	19	1
2	35	1	18	22	1
3	5	1	19	29	1
3	7	1	20	29	1
3	9	1	21	23	1
4	27	1	22	29	1
4	35	1	23	24	1
5	11	1	24	25	1
6	8	1	25	30	1
6	31	1	25	32	1
7	17	1	26	23	1
8	10	1	27	28	1
9	21	1	28	33	1
10	14	1	30	33	1
10	16	1	31	19	1
10	18	1	31	29	1
11	13	1	32	29	1
12	14	1	33	34	1
12	16	1	34	29	1
13	15	1	35	26	1

Following Fig. 2 and Table 1, in total 30 signaling networks were organized into the data required. Table 2 shows the other 28 signaling pathway networks used in present study, besides JNK-pathway and VEGF-pathway networks discussed in the following analysis.

Table 2 Twenty-eight signaling pathway networks (Source: www.sabiosciences.com)

akt-signaling	BRCA1-pathway
TNF-Signaling	Caspase-Cascade
ppar-pathway	Androgen-Signaling
p53-signaling	PTEN-Pathway
STAT3-pathway	MAPK-Signaling
PI3K signaling	mTOR-Pathway
Ras Pathway	JAK-STAT-Pathway
Mitochondrial-Apoptosis	HIF1Alpha-Pathway
ErbBfamily-Pathway	IGF1R_Signaling
TGF-Beta pathway	Fas-Signaling
EGF-pathway	ERK_Signaling
Inerferon-Pathway	cAMP-Dependent
Estrogen-Pathway	Cellular_Apoptosis
HGF-pathway	Cyclins+Cell_Cycle_Regulatio

2.2 Methods

Methods used in present study came from Zhang (2012b), Zhang and Zhan (2011). Suppose that the portion of nodes with k-degree is p_k, the degree will thus be a random variable and its distribution is degree distribution.

In present algorithm, in addition to power law distribution, binomial distribution, Poisson distribution, and exponential distribution, some other indices and methods were also used to detect network type (Zhang and Zhan, 2011; Zhang, 2012b):

(1) Coefficient of variation. In a random network, the majority of nodes have the same degree as the average. The coefficient of variation, H, can be used to describe the type of a network (Zhang and Zhan, 2011; Zhang, 2012b):

$$H=s^2/\bar{u},\ \bar{u}=\sum d_i/v,\ s^2=\sum(d_i-\bar{u})^2/(v-1),$$

where $\bar{u}$, s^2: mean and variance of degree; v: number of nodes; d_i: the degree of node i, i=1,2,...,v. The network is a random network, if $H\leq 1$. Calculate $\chi^2=(v-1)H$, and if $\chi_{1-\alpha}^2(v-1)<\chi^2<\chi_{\alpha}^2(v-1)$, the network is a complete random network. It is a complex network, if $H>1$, and to some extent, network complexity increases with H.

As defined in Zhang and Zhan (2011), $E=s^2-\bar{u}$, is the entropy of network. A more complex network has the larger entropy. If $E\leq 0$ the network is a random network and it is a complex network if $E>0$.

(2) Aggregation index. Network type can be determined by using the following aggregation index (Zhang and Zhan, 2011; Zhang, 2012b):

$$H=v*\sum d_i(d_i-1)/[\sum d_i(\sum d_i-1)].$$

The network is a random network, if $H\leq 1$. Calculate $\chi^2=H(\sum d_i-1)+v-\sum d_i$, and if $\chi^2<\chi_{\alpha}^2(v-1)$, the network is a complete random network. It is a complex network if $H>1$, and network complexity increases with H.

The Java algorithm, netType (http://www.iaees.org/publications/software/index.asp, BioNetAnaly), was used to calculate degree distribution and detect network type.

3 Results

3.1 VEGF-pathway (Matsumoto and Claesson-Welsh, 2001)

From the statistics in Table 3, we found that ANGIO GENESIS has the most connections. It is likely the most significant metabolite/step in VEGF-pathway, seconded by Akt/PKB and Actin Reorganization.

Table 3 Degree distribution statistics of VEGF-pathway (collated from Table 1)

Rank	Metabolite /step	Degree	Rank	Metabolite /step	Degree
1	29	6	19	4	2
2	10	4	20	5	2
3	31	4	21	9	2
4	2	3	22	11	2
5	3	3	23	12	2
6	6	3	24	13	2
7	7	3	25	15	2
8	8	3	26	17	2
9	14	3	27	18	2
10	16	3	28	21	2
11	19	3	29	22	2
12	20	3	30	24	2
13	23	3	31	26	2
14	25	3	32	28	2
15	27	3	33	30	2
16	33	3	34	32	2
17	35	3	35	34	2
18	1	2			

Use the data in Table 1, and run the netType as the following:

C:\ BioNetAnaly\bin>java netType VEGF

We thus obtained the results for degree distribution and network type as follows:

Aggregation index of the network: 0.7274247491638796
It is a random network.
Variation coefficient H of the network: 0.2704603580562659
Entropy E of the network: -1.9176470588235297
It is a random network.
Binomial distribution Chi-square=82.10062003702488
Binomial p=0.12063492063492064
It is likely not a random network
Poisson distribution chi-square=119.20494737910627
Poisson lamda=2.6285714285714286
It is likely not a random network
Exponential distribution lamda=0.3804347826086957
It is not an exponential network
Power law distribution KS D value=0.0
Degrees are power law distributed, it is A scale-free complex network
Power law alpha=NaN
Power law xmin=6

It can be found that the VEGF-pathway network is a random network in terms of aggregation index, coefficient of variation and network entropy. Binomial and Poisson distribution fitting results showed that this network does not meet the above two distribution patterns. In general, the degree is power law distributed and the VEGF-pathway network is most likely a scale-free complex network.

3.2 JNK-pathway (Himes et al., 2006)

Following the above procedures, JNK-pathway in Fig. 2 was finally transformed into the data used in netType program after each metabolite/step was given an ID (Table 4), as shown in Table 5.

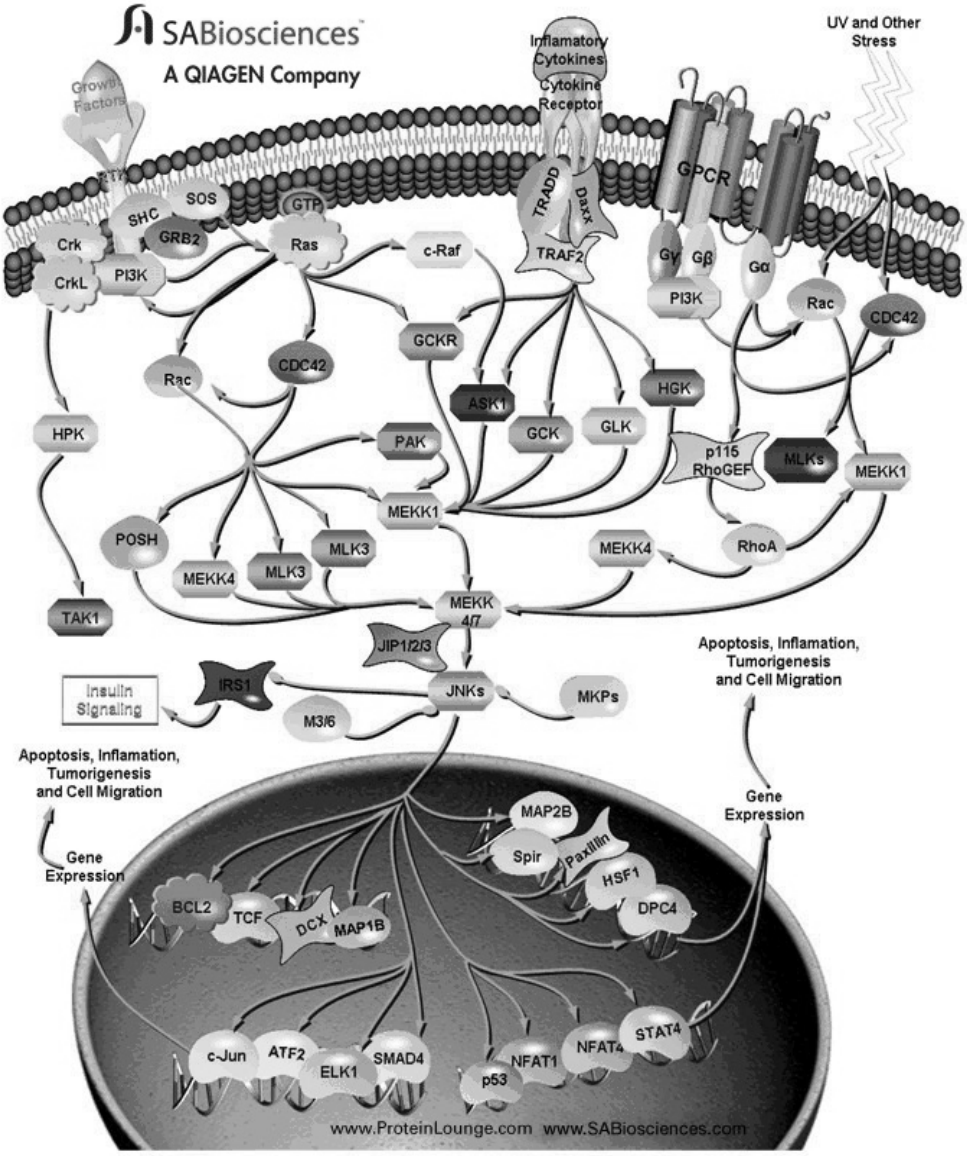

Fig. 2 JNK-pathway (Source: www.sabiosciences.com)

Table 4 IDs for metabolite/steps in JNK-pathway

ID	**Metabolite/Step**	ID	**Metabolite/Step**
1	TRAF2	25	MLKs
2	CrkL	26	MEKK4/7
3	HPK	27	JNKs
4	TAK1	28	M3/6
5	Ras-GTP	29	MKPs
6	GCKR	30	IRS1
7	CDC42	31	BCL2
8	ASK1	32	TCF
9	c-Raf	33	DCX
10	GCK	34	MAP1B
11	Rac	35	Spir
12	GLK	36	MAP2B
13	MKK1	37	HSF1
14	HGK	38	DPC4
15	PAK	39	Paxillin
16	MLK3	40	c-Jun
17	GRB2-SOS-SHC	41	ATF2
18	GPCR	42	ELK1
19	PI3K	43	SMAD4
20	UV and other stress	44	p53
21	MEKK4	45	NFAT1
22	POSH	46	NFAT4
23	p115RhoGEF	47	STAT4
24	RhoA	48	Gene Expression

Table 5 The data of JNK-pathway used in netType program

ID for from metabolite/step	**ID for to metabolite/step**	**Relation -ship**	**ID for from metabolite/step**	**ID for to metabolite/step**	**Relation -ship**
1	6	1	20	11	1
1	8	1	21	26	1
1	10	1	22	26	1
1	12	1	24	13	1
1	14	1	24	21	1
2	3	1	23	24	1
3	4	1	26	27	1
5	6	1	27	30	1
5	9	1	27	31	1
5	7	1	27	32	1
5	11	1	27	33	1
5	19	1	27	34	1
6	13	1	27	35	1
7	13	1	27	36	1

7	15	1	27	37	1
7	16	1	27	38	1
7	21	1	27	39	1
7	22	1	27	40	1
7	11	1	27	41	1
7	25	1	27	42	1
8	13	1	27	43	1
9	8	1	27	44	1
10	13	1	27	45	1
11	13	1	27	46	1
11	15	1	27	47	1
11	16	1	28	27	1
11	21	1	29	27	1
11	22	1	35	48	1
11	25	1	36	48	1
12	13	1	37	48	1
13	26	1	38	48	1
14	13	1	39	48	1
15	13	1	40	48	1
16	26	1	41	48	1
17	5	1	42	48	1
18	7	1	43	48	1
18	11	1	44	48	1
18	23	1	45	48	1
19	5	1	46	48	1
19	11	1	47	48	1
20	7	1			

From the statistics in Table 6, we found that JNKs has the most connections. JNKs is likely the most significant metabolite/step in JNK-pathway.

Table 6 Degree distribution statistics of JNK-pathway (collated from Table 5)

Rank	Metabolite /step	Degree	Rank	Metabolite /step	Degree
1	27	21	25	25	2
2	48	13	26	35	2
3	11	11	27	36	2
4	7	10	28	37	2
5	13	10	29	38	2
6	5	7	30	39	2
7	1	5	31	40	2
8	26	5	32	41	2
9	21	4	33	42	2
10	6	3	34	43	2
11	8	3	35	44	2
12	15	3	36	45	2

13	16	3	37	46	2
14	18	3	38	47	2
15	19	3	39	2	1
16	22	3	40	4	1
17	24	3	41	17	1
18	3	2	42	28	1
19	9	2	43	29	1
20	10	2	44	30	1
21	12	2	45	31	1
22	14	2	46	32	1
23	20	2	47	33	1
24	23	2	48	34	1

Use the data in Table 5 and run the netType. We obtained the results for degree distribution and network type as the follows:

Aggregation index of the network: 1.950943396226415
It is a complex network.
Variation coefficient H of the network: 4.2170212765957515
Entropy E of the network: 10.723404255319172
It is a complex network.
Binomial distribution Chi-square=1703.3646822209705
Binomial p=0.0763888888888889
It is likely not a random network
Poisson distribution chi-square=564.9845392902733
Poisson lamda=3.3333333333333335
It is likely not a random network
Exponential distribution lamda=0.3
It is not an exponential network
Power law distribution KS D value=0.0
Degrees are power law distributed, it is A scale-free complex network
Power law alpha=NaN
Power law xmin=21

The results showed that JNK-pathway network is most likely A scale-free complex network.

3.3 Results for other 28 signaling metabolic networks

Table 7 indicates the results of network type detection for remaining 28 signaling networks.

Table 7 Summary of results for network type detection of 28 signaling networks

	akt-signaling	**TNF-Signaling**	**ppar-pathway**	**p53-signaling**
Aggregation index of the network	4.52621596	0.892721519	0.728186145	1.951279528
Variation coefficient *H* of the network	8.485475985	0.7175	0.362282878	3.368872549
Entropy *E* of the network	15.74531155	-0.729032258	-1.464387464	5.83107089

Binomial distribution Chi-square (χ^2)	7.550775793	185.2217856	61.78265951	636313.367
Binomial *p*	0.007662835	0.279569892	0.283950617	0.051282051
Poisson distribution Chi-square (χ^2)	356.3078645	41.45697612	56.839442	316.086834
Poisson λ	2.103448276	2.580645161	2.296296296	2.461538462
Exponential distribution λ	0.475409836	0.3875	0.435483871	0.40625
Power law distribution K-S *D* value	0	0	0	0
Power law α	NaN	Infinity	Infinity	NaN
Power law x_{min}	32	6	4	17
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network
	STAT3-pathway	**PI3K signaling**	**Ras Pathway**	**Mitochondrial-Apoptosis**
Aggregation index of the network	0.868778	1.124764151	1.05614035	1.054945055
Variation coefficient *H* of the network	0.70903	1.354241071	1.12383901	1.146520147
Entropy *E* of the network	-0.630435	0.994360902	0.26890756	0.384615385
Binomial distribution Chi-square (χ^2)	41.00305	31.8895742	2.24869397	50.1063552
Binomial *p*	0.157407	0.276803119	0.1015873	0.155555556
Poisson distribution Chi-square (χ^2)	25.78968	8.993995609	29.3818551	51.19489909
Poisson λ	2.166667	2.807017544	2.17142857	2.625
Exponential distribution λ	0.461538	0.35625	0.46052632	0.380952381
Power law distribution K-S *D* value	0	0	0	0
Power law α	Infinity	Infinity	NaN	NaN
Power law x_{min}	5	9	10	10
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network
	ErbBfamily Pathway	**TGF-Beta pathway**	**EGF-pathway**	**Inerferon Pathway**
Aggregation index of the network	0.769231	0.915662651	1.18505218	0.664335664
Variation coefficient *H* of the network	0.382353	0.810810811	1.45577667	0.239819005

Entropy *E* of the network	-1.623529	-0.418207681	1.11043771	-1.694117647
Binomial distribution Chi-square (χ^2)	82.68389	1497.027453	4.67977985	112.6795217
Binomial *p*	0.320635	0.239766082	0.04646465	0.380952381
Poisson distribution Chi-square (χ^2)	62.14559	120.87115	257.481508	208.9204611
Poisson λ	2.628571	2.210526316	2.43636364	2.228571429
Exponential distribution λ	0.380435	0.452380952	0.41044776	0.448717949
Power law distribution K-S *D* value	0	0	0	0
Power law α	Infinity	NaN	NaN	NaN
Power law x_{min}	5	6	14	4
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network
	Estrogen Pathway	**HGF-pathway**	**BRCA1-pathway**	**Caspase-Cascade**
Aggregation index of the network	2.139322	0.972972973	1.98043326	2.199460916
Variation coefficient *H* of the network	3.650161	0.943629344	3.07851852	3.862349914
Entropy *E* of the network	6.089732	-0.115873016	4.31692308	6.742424242
Binomial distribution Chi-square (χ^2)	15.90759	8414.563824	0.23396135	56.05705936
Binomial *p*	0.026005	0.101851852	0.01282051	0.017283951
Poisson distribution Chi-square (χ^2)	264.2854	40.13860056	125.876825	315.0779746
Poisson λ	2.297872	2.055555556	2.07692308	2.355555556
Exponential distribution λ	0.435185	0.486486486	0.48148148	0.424528302
Power law distribution K-S *D* value	0	0	0	0
Power law α	NaN	NaN	NaN	NaN
Power law x_{min}	20	8	14	21
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network
	Androgen-Signaling	**PTEN-Pathway**	**MAPK-Signaling**	**mTOR-Pathway**
Aggregation index of the network	1.079193	1.126506024	1.30956625	0.987677371
Variation coefficient *H* of the network	1.237579	1.328125	1.83094099	0.971794872
Entropy *E* of the network	0.695767	0.835227273	2.20629159	-0.063768116

Binomial distribution Chi-square (χ^2)	5.065875	71.87522136	197056.514	75.54143044
Binomial *p*	0.178571	0.141414141	0.16475096	0.128019324
Poisson distribution Chi-square (χ^2)	23.78943	29.71517195	100.314801	39.29714189
Poisson λ	2.928571	2.545454545	2.65517241	2.260869565
Exponential distribution λ	0.341463	0.392857143	0.37662338	0.442307692
Power law distribution K-S *D* value	0	0	0	0
Power law α	NaN	NaN	NaN	NaN
Power law x_{min}	10	10	11	9
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network

	JAK-STAT-Pathway	**HIF1Alpha-Pathway**	**IGF1R-Signaling**	**Fas-Signaling**
Aggregation index of the network	0.982304	2.090909091	0.81334445	1.47242921
Variation coefficient *H* of the network	0.953231	3.210526316	0.54787879	2.120861459
Entropy *E* of the network	-0.121816	4.421052632	-1.0811594	2.629713424
Binomial distribution Chi-square (χ^2)	306.7507	12.46450871	49.8289811	4.708626886
Binomial *p*	0.165375	0.022792023	0.19323671	0.051282051
Poisson distribution Chi-square (χ^2)	45.76475	170.5548778	35.2204129	314.8308315
Poisson λ	2.604651	2	2.39130435	2.346153846
Exponential distribution λ	0.383929	0.5	0.41818182	0.426229508
Power law distribution K-S *D* value	0	0	0	0
Power law α	NaN	NaN	NaN	NaN
Power law x_{min}	9	16	7	13
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network

	ERK-Signaling	**cAMP-Dependent**	**Cellular-Apoptosis**	**Cyclins+Cell_ Cycle-Regulation**
Aggregation index of the network	2.061591	2.025092672	1.13825609	1.296023564
Variation coefficient *H* of the network	4.004843	3.593795094	1.38308458	1.844537815
Entropy *E* of the network	8.413559	6.503844414	1.04761905	2.364705882

Binomial distribution Chi-square (χ^2)	23231.23	845.7420426	58.8993924	8474.914866
Binomial *p*	0.046296	0.019900498	0.17006803	0.193650794
Poisson distribution Chi-square (χ^2)	462.1018	595.3938607	57.7338769	102.7538674
Poisson λ	2.8	2.507462687	2.73469388	2.8
Exponential distribution λ	0.357143	0.398809524	0.36567164	0.357142857
Power law distribution K-S *D* value	0	0	0	8
Power law α	NaN	NaN	NaN	Infinity
Power law x_{min}	23	23	11	8
Type of degree distribution	Power law	Power law	Power law	Power law
Network type	A scale-free complex network	A scale-free complex network	A scale-free complex network	A scale-free complex network

4 Discussion

All 30 kinds of tumor signaling metabolic networks are basically scale-free complex networks. Most degree distributions are power law distribution and exponential distribution, indicating that a few metabolites/steps have high degree, and the degree of the majority metabolites/steps is low. The metabolites/steps with higher degree (more connections) are often key metabolites or metabolic processes.

Our results showed that 11 kinds of networks, including VEGF and ppar, have the coefficient of variation of less than 1, and the rest of 19 kinds of networks have coefficient of variation of greater than 1. It demonstrates that the 11 kinds of networks are more random than the other 19 kinds of metabolic networks.

Most studies on degree distribution and structure of networks (Cohen et al., 1990; Pimm et al., 1991; Havens, 1992; Martinez, 1992; Zhang, 2011) have focused on food webs and ecological networks. For metabolic networks this area is relatively weak and should be strengthened in the future.

Due to the limitation of the program we used, we have only made analysis on undirected networks. In the future studies, directed networks should be analyzed and more methods and tools should be used to approach tumor signaling pathways (Zhang, 2012b).

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