

# 生物分子网络实践



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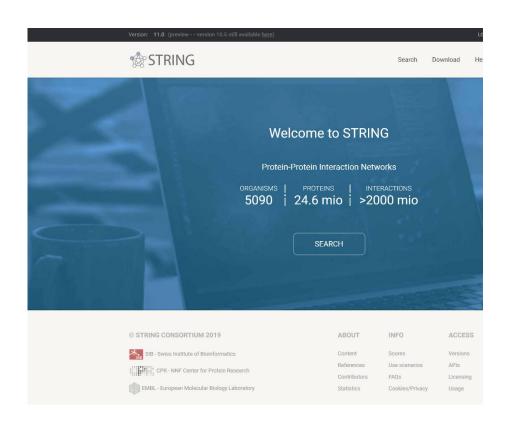
2019年4月23日

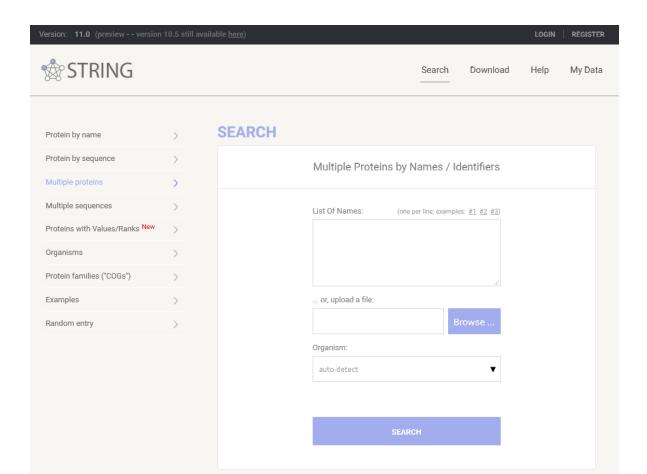
- 第一节: 软件的演示
- 第二节: 分组练习
- 第三节: 分组汇报
- 第四节: 总结

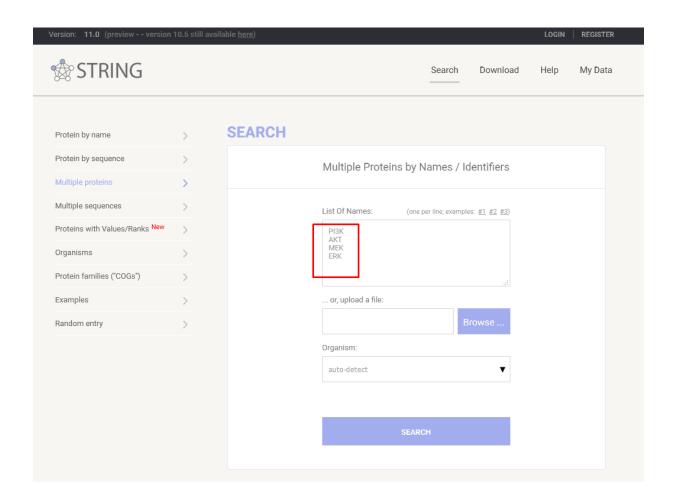
# 第一节: 软件的演示

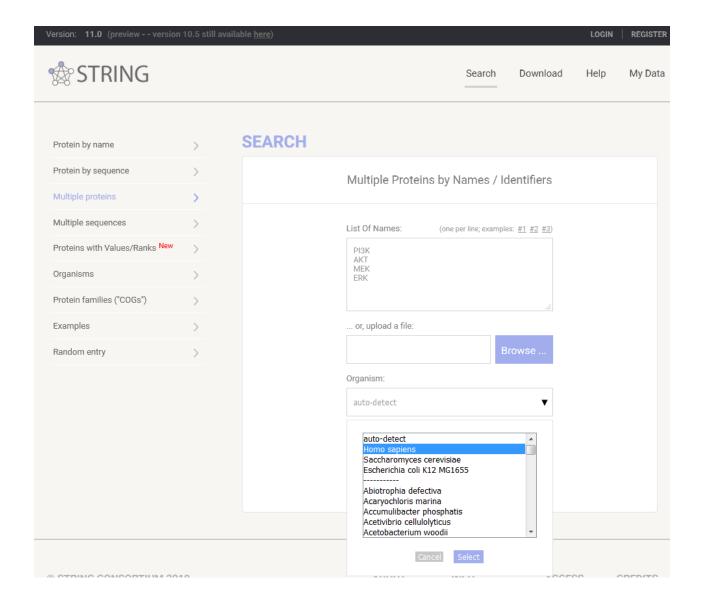
## String

https://string-db.org/cgi/input.pl?sessionId=2d9PS5Co25Df&input\_page\_show\_search=off











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The following proteins in *Homo sapiens* appear to match your input. Please review the list, then click 'Continue' to proceed.

<- BACK

CONTINUE ->

'PI3K':
PIK3CA - Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4- phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5- bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to [] [a.k.a. AAI13602.1, HPA009985, CCDS43171, PI3K]
PIK3CB - Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4- phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5- bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Involved in the activation of AKT1 upon stimulatio [] [a.k.a. PIK3C1, CAH18210.1, OTTHUMP00000216908, PI3K]
PIK3CG - Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Links G-protein coupled receptor activation to PIP3 production. Involved in immune, inflammatory and allergic responses. Modulates [] [a.k.a. NP_001269355, NM_001282426.1, UPI000187920A, PI3K]
PIK3CD - Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PftdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Mediates immune responses. Plays a role in B-cell development, proliferation, migration, and function. Required for B-cell recept [] [a.k.a. NM_005026, 578F, OTTHUMT00000004237, PI3K]
PIK3AP1 - Phosphoinositide 3-kinase adapter protein 1; Signaling adapter that contributes to B-cell development by linking B-cell receptor (BCR) signaling to the phosphoinositide 3-kinase (Pi3K)-Akt signaling pathway. Has a complementary role to the BCR coreceptor CD19, coupling BCR and Pi3K activation by providing a docking site for the Pi3K subunit PIK3R1. Alternatively, links Toll-like receptor (TLR) signaling to Pi3K activation, a process preventing excessive inflammatory cytokine production. Also involved in the activation of Pi3K in natural killer cells. May be involved in the survival of [] [a.k.a. BCAP, BC029917, Q8NAC8]
NYAP2 - Neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adapter 2; Activates PI3K and concomitantly recruits the WAVE1 complex to the close vicinity of PI3K and regulates neuronal morphogenesis [a.k.a. KIAA1486, XM_005246708, Q9P242]

















Less

#### **Network Stats**

number of nodes: 4 number of edges: 6

average node degree: 3 avg. local clustering coefficient: 1

expected number of edges: 3 PPI enrichment p-value: 0.0319

your network has significantly more interactions than expected (<u>what does that mean?</u>)

#### Functional enrichments in your network

	Biological Process (G0)		
GO-term	description	count in gene set	false discovery rate
GO:0051052	regulation of DNA metabolic process	4 of 381	0.00011
GO:0038127	ERBB signaling pathway	3 of 72	0.00011
GO:0032147	activation of protein kinase activity	4 of 347	0.00011
GO:0043276	anoikis	2 of 10	0.00032
GO:0097011	cellular response to granulocyte macrophage colony-stimul	2 of 11	0.00033
			(more)

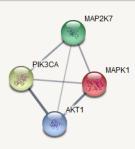
	Molecular Function (GO)		
GO-term	description	count in gene set	false discovery rate
GO:0004712	protein serine/threonine/tyrosine kinase activity	3 of 42	3.45e-06
GO:0004674	protein serine/threonine kinase activity	4 of 444	1.03e-05
GO:0019902	phosphatase binding	3 of 168	4.54e-05
GO:0004708	MAP kinase kinase activity	2 of 15	4.62e-05
GO:0005524	ATP binding	4 of 1462	0.00026
			(more )

	Reference publications		
publication	(year) title	count in gene set	false discovery rate
PMID:29632655	(2018) Novel approaches against epidermal growth factor r	4 of 13	3.82e-08
PMID:29534015	(2018) Targeting Hodgkin and Reed-Sternberg Cells with an	4 of 35	3.82e-08
PMID:29492189	(2018) Distinct histone modifications denote early stress-in	4 of 29	3.82e-08
PMID:29401696	(2018) PIM Kinases and Their Relevance to the PI3KAKTmT	4 of 27	3.82e-08
PMID:29623959	(2017) A network modeling approach to elucidate drug resi	4 of 30	3.82e-08
			(more)

	KEGG Pathways		
pathway	description	count in gene set	false discovery rate
hsa04664	Fc epsilon RI signaling pathway	4 of 67	1.99e-08
hsa04012	ErbB signaling pathway	4 of 83	2.28e-08



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#### Export your current network:

... as a bitmap image: download file format is 'PNG': portable network graphic

... as a high-resolution bitmap: download same PNG format, but resolution at 400 dpi

... as a vector graphic: download SVG: scalable vector graphic - can be opened and edited in Illustrator, CorelDraw, Dia, etc

... as simple tabular text output: download TSV: tab separated values - can be opened in Excel

... as an XML summary: download structured XML interaction data, according to the 'PSI-MI' data standard

... network coordinates: download a flat-file format describing the coordinates and colors of nodes in the network

... protein sequences: download MFA: multi-fasta format - containing the aminoacid sequences in the network

... protein annotations: download a tab-delimited file describing the names, domains and annotated functions of the network proteins

#### Browse interactions in tabular form:

<u>^node1</u>	node2	node1 accession	node2 accession	node1 annotation	node2 annotation	score
AKT1	MAP2K7	ENSP00000451828	ENSP00000381070	RAC-alpha serine/threonine-prot	Dual specificity mitogen-activate	0.468
AKT1	MAPK1	ENSP00000451828	ENSP00000215832	RAC-alpha serine/threonine-prot	Mitogen-activated protein kinase	0.905
AKT1	PIK3CA	ENSP00000451828	ENSP00000263967	RAC-alpha serine/threonine-prot	Phosphatidylinositol 4,5-bisphos	0.998
MAP2K7	AKT1	ENSP00000381070	ENSP00000451828	Dual specificity mitogen-activate	RAC-alpha serine/threonine-prot	0.468
MAP2K7	MAPK1	ENSP00000381070	ENSP00000215832	Dual specificity mitogen-activate	Mitogen-activated protein kinase	0.645
MAP2K7	PIK3CA	ENSP00000381070	ENSP00000263967	Dual specificity mitogen-activate	Phosphatidylinositol 4,5-bisphos	0.698
MAPK1	AKT1	ENSP00000215832	ENSP00000451828	Mitogen-activated protein kinase	RAC-alpha serine/threonine-prot	0.905
MAPK1	MAP2K7	ENSP00000215832	ENSP00000381070	Mitogen-activated protein kinase	Dual specificity mitogen-activate	0.645
MAPK1	PIK3CA	ENSP00000215832	ENSP00000263967	Mitogen-activated protein kinase	Phosphatidylinositol 4,5-bisphos	0.603
PIK3CA	AKT1	ENSP00000263967	ENSP00000451828	Phosphatidylinositol 4,5-bisphos	RAC-alpha serine/threonine-prot	0.998
PIK3CA	MAP2K7	ENSP00000263967	ENSP00000381070	Phosphatidylinositol 4,5-bisphos	Dual specificity mitogen-activate	0.698
PIK3CA	MAPK1	ENSP00000263967	ENSP00000215832	Phosphatidylinositol 4,5-bisphos	Mitogen-activated protein kinase	0.603

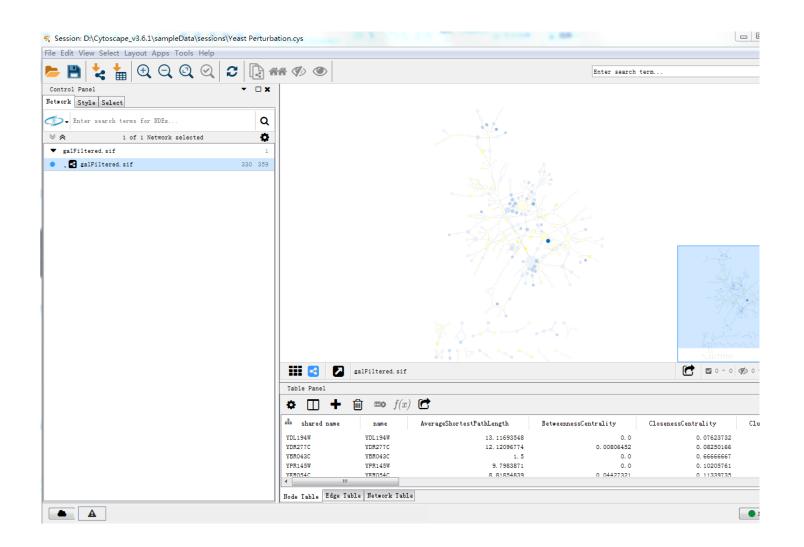
## Cytoscape

https://cytoscape.org/



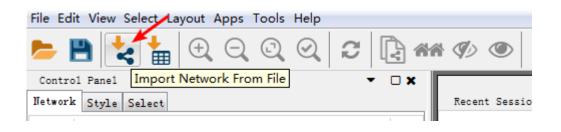
Cytoscape is an open source software platform for visualizing complex networks and integrating these with any type of attribute data. A lot of *Apps* are available for various kinds of problem domains, including bioinformatics, social network analysis, and semantic web. Learn more...





## 构建网络 导入数据构建网络

1、File->Import->Network-->File;或者直接点击快捷选项.

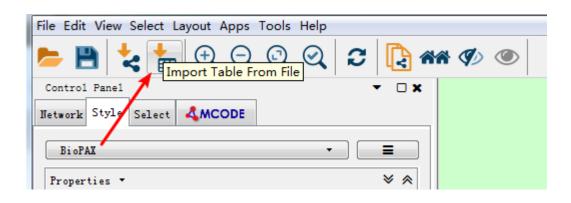


- 2、选择你要建立连接的两列,Source列为自身id, target列为当前id所在的簇
- 3、设置好之后点击 OK

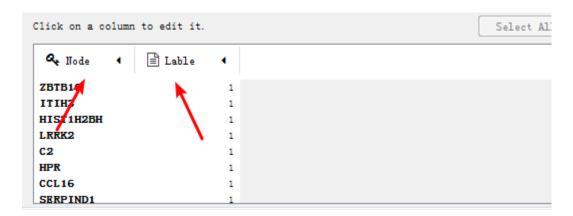


## 导入Lable文件(也就是后面提到的Column选择的对象)

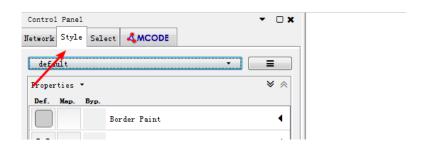
1、导入节点属性File->Import-> Table 选择需要导入的属性文件(如选择每个节点对应的簇)点击 import,或者直接点击快捷选项.



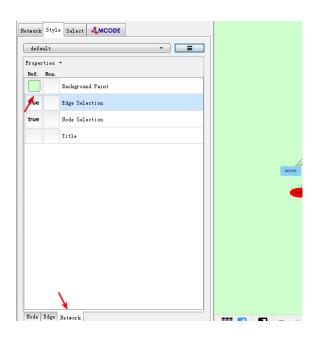
## 2、默认设置,点击OK



## 设置网络风格 Control Panel -> Style



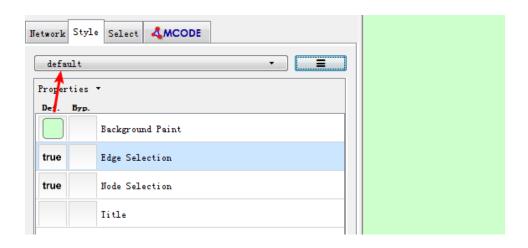
## 1、Style —>Network—>对整个 网络风格进行设置 设置背景颜色



整体网络风格 点击 default可以选择合适的风格,如 BioPAX

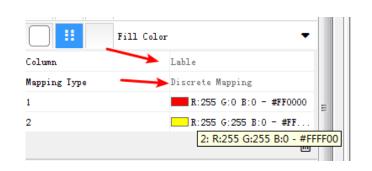


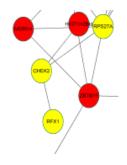
## 整体网络风格 点击 default可以选择合适的风格,如 BioPAX



2、如设置Node的颜色 Style —>Node(一般默认)—>Fill Color

## 2、如设置Node的颜色 Style —>Node(一般默认)—>Fill Color

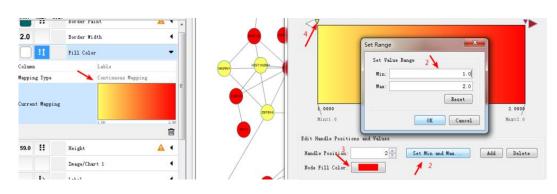




## 备注:

Column: 选择要涂上颜色的对象可以是单个、几个或者一簇,多簇; Mapping Type: 主要有三种类型,Continuous、Discrete 和 Passthrough

## 如选择Continuous类型(因为这里只有两簇,所以min=1,max=2)



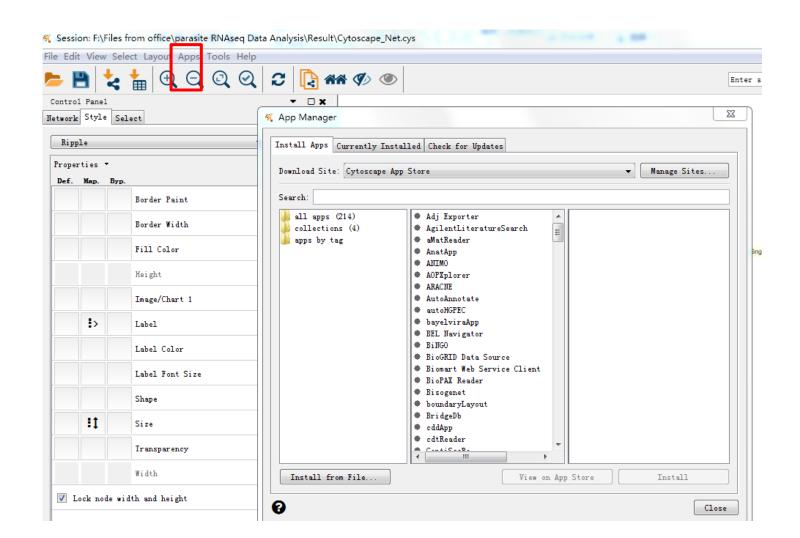
## 3、如设置Node的形状 Style —>Node(一般默认)—>Shape

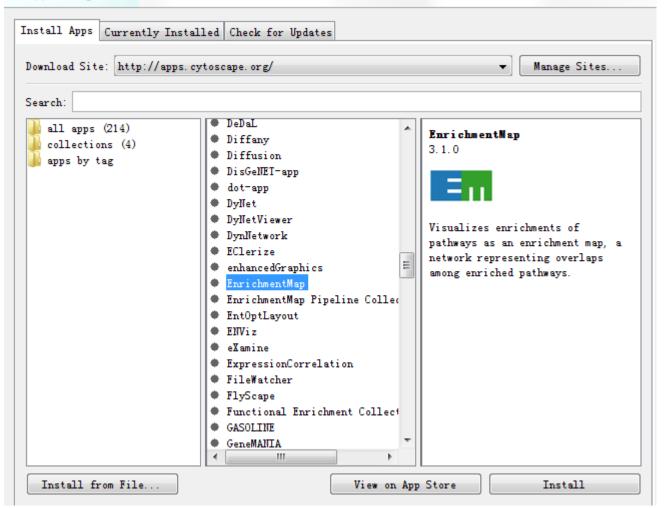


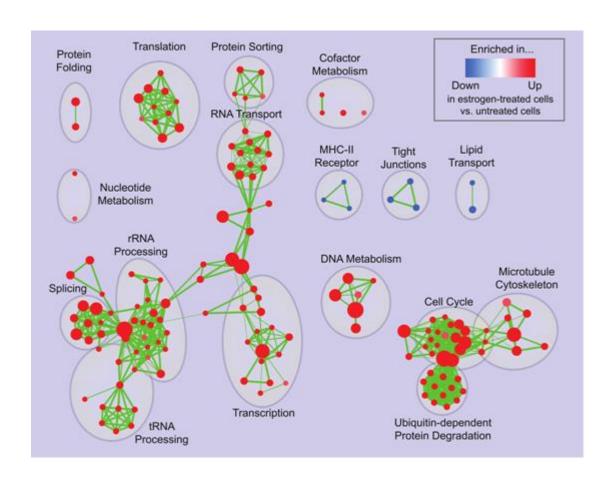
4、Style —>Edge—>对边的风格进行设置(一般不需要)

注意:如果需要对整体网络风格进行设置的话,建议先进行整体网络风格的设置,因为设置完这个网络风格之后,之前选择的对Node/Edge的设置都会消失。。。

5、Style ->自由发挥设置你喜欢的网络风格。

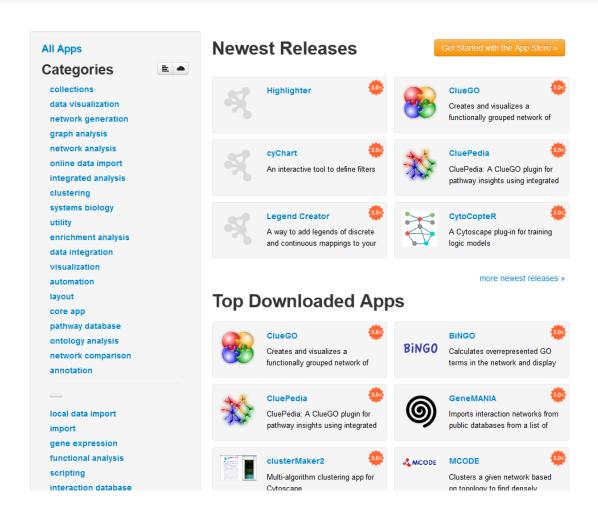






Search the App Store

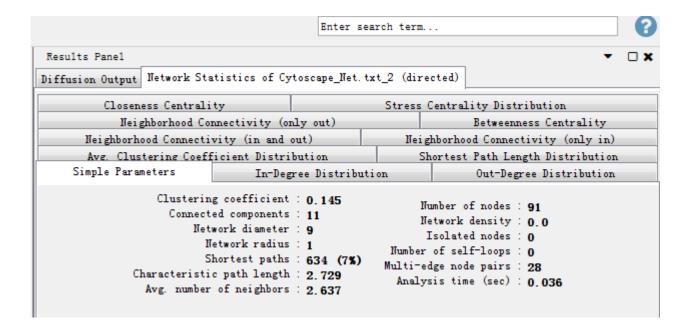




# Cytoscape APP的使用

- 1 Centiscape
- 2 CytoHubba
- 3 Enrichment Map
- 4 iRegulon
- 5 DisGeNET 1
- 6 DisGeNET 2
- 7 ExpressionCorrelation
- 8 GRNCOP2

## Cytoscape $\rightarrow$ Tools $\rightarrow$ NetworkAnalyzer $\rightarrow$ Analyze Network



# 第二节: 分组练习

## 案例:

寄生虫感染小鼠的脑组织后第0,2,7,14,21天的RNA-seq基因表达谱(已分析DEGs)

(https://github.com/dongbusun/Bioinformatics\_Teaching\_Bionetwork/DEGs.xls)

## 任务:

## 分组1:

使用string数据库构建PPI网络;进行功能富集分析;导出网络结构的数据。 使用Cytoscape对以上导出的网络数据进行绘制、网络分析。

## 分组2:

使用Cytoscape APP(如ExpressionCorrelation)构建基因相关网络,并进一步分析。

## 分组3:

使用Cytoscape APP (如GRNCOP2等)构建基因调控网络,并进一步分析。

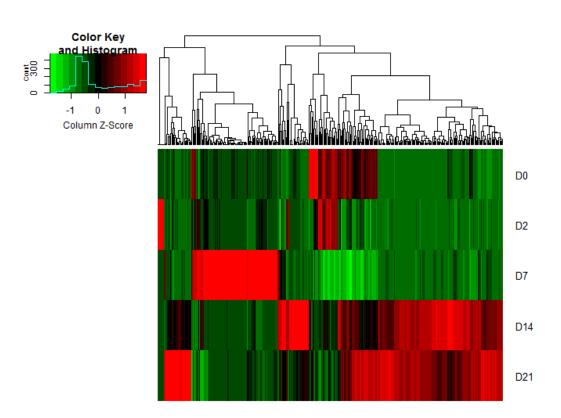
## 分组4:

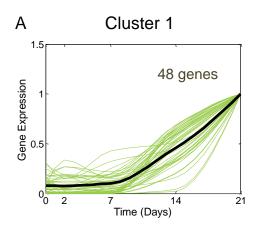
编制程序(如R语言等)构建共表达网络,并使用Cytoscape可视化和进一步分析。

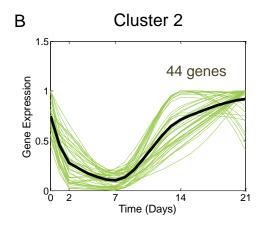
注意: 生物学意义的解释。

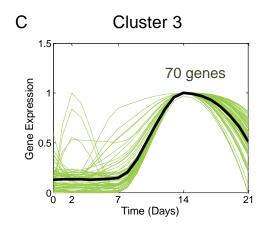
# 第三节: 分组汇报

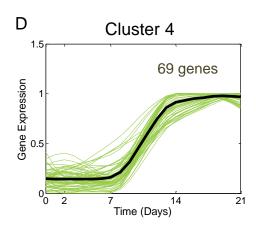
# 第四节: 拓展讲解

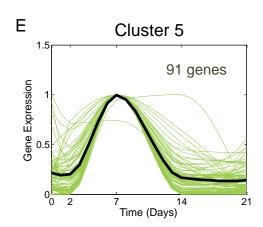


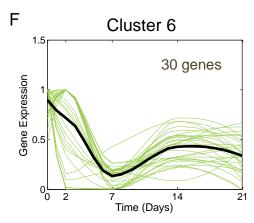


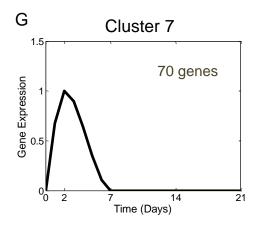


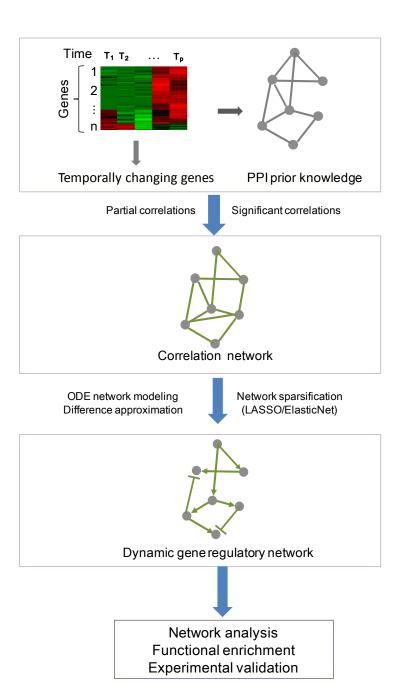


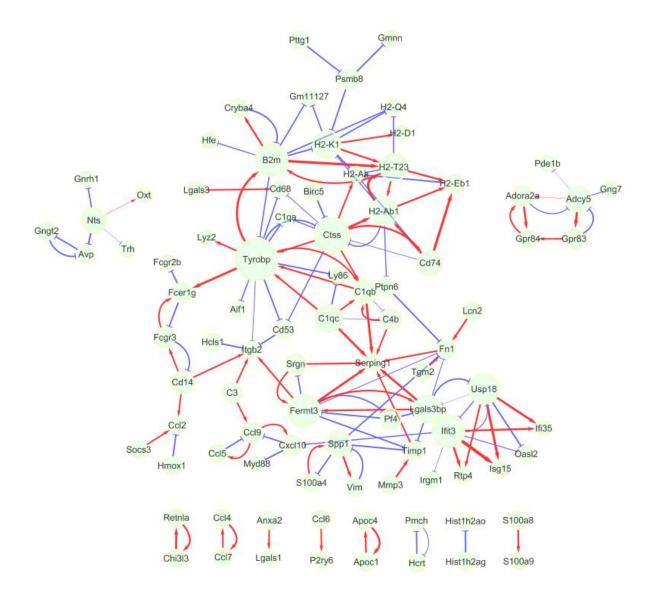










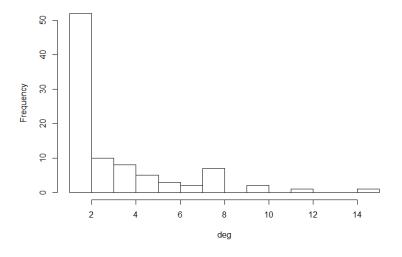


## Degree

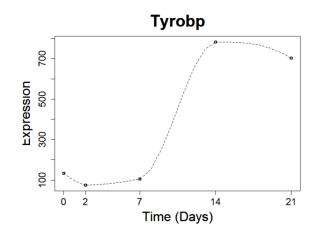
Mmp3	Ccl6	Anxa2	Birc5	Tgm2	Hmox1	Socs3	Hcls1	Lgals3	S100a8	Pttg1	Hist1h2ag	Lcn2	Hfe
1	1	1	1	1	1	1	1	1	1	1	1	1	1
Myd88	Fcgr2b	Gng7	Pde1b	lrgm1	Gnrh1	Oxt	Trh	Gmnn	P2ry6	Lgals1	Lyz2	Aif1	H2-D1
1	1	1	1	1	1	1	1	1	1	1	1	1	1
S100a9	Hist1h2ao	Hcrt	Ccl5	Apoc1	Pmch	C3	Gngt2	Ccl7	Chi3l3	Retnla	Apoc4	Ptpn6	Vim
1	1	2	2	2	2	2	2	2	2	2	2	2	2
Ccl4	Cryba4	S100a4	Gm11127	C1qa	lsg15	Rtp4	Oasl2	Ifi35	Ly86	Avp	Pf4	Srgn	Gpr84
2	2	2	2	2	2	2	2	2	2	3	3	3	3
Psmb8	Cd53	Gpr83	H2-Q4	Cd68	Ccl2	Cxcl10	H2-Eb1	C4b	Fcer1g	Cd14	Fcgr3	Nts	Adora2a
3	3	3	3	3	3	4	4	4	4	4	4	4	4
Cd74	Ccl9	C1qc	Timp1	H2-Aa	Adcy5	Spp1	ltgb2	C1qb	Fn1	H2-T23	H2-Ab1	Usp18	Lgals3bp
5	5	5	5	5	6	6	6	7	7	8	8	8	8
Ifit3	H2-K1	Serping1	B2m	Fermt3	Ctss	Tyrobp							
8	8	8	10	10	12	15							

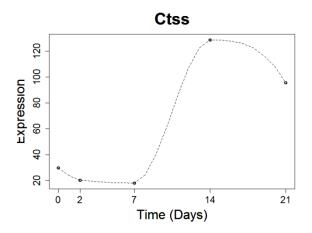
# # Degree deg <- degree(net, mode="all") sort(deg) ## Hubs hs <- hub\_score(net, weights=NA)\$vector which(hs==max(hs)) # Tyrobp</pre>

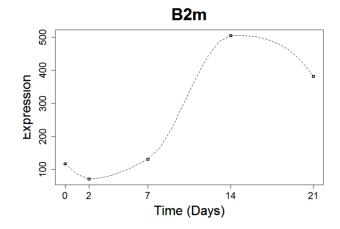
#### Histogram of node degree

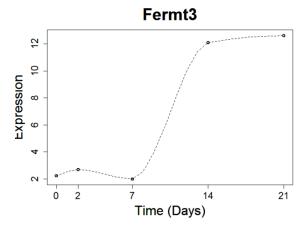


## Expression profile of hub genes









## Gene Card summary

TYROBP (TYRO Protein Tyrosine Kinase Binding Protein) is a Protein Coding gene. Diseases associated with TYROBP include Nasu-Hakola Disease and Tyrobp-Related Polycystic Lipomembranous Osteodysplasia With Sclerosing Leukoencephalopathy. Among its related pathways are Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell and Immune System. GO annotations related to this gene include identical protein binding and signal transducer activity, downstream of receptor. In the central nervous system, the complex TYROBP-TREM2 appears to play an important role in immune cells called microglia. These cells protect the brain and spinal cord from foreign invaders and remove dead nerve cells and other debris.

CTSS (Cathepsin S) is a Protein Coding gene. Diseases associated with CTSS include Mandibular Cancer and Cercarial Dermatitis. Among its related pathways are G-protein signaling N-RAS regulation pathway and Immune System. GO annotations related to this gene include peptidase activity and cysteine-type peptidase activity. An important paralog of this gene is CTSK.

B2M (Beta-2-Microglobulin) is a Protein Coding gene. Diseases associated with B2M include Hypoproteinemia, Hypercatabolic and Variant Abeta2m Amyloidosis. Among its related pathways are Interferon gamma signaling and Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell. GO annotations related to this gene include identical protein binding.

FERMT3 (Fermitin Family Member 3) is a Protein Coding gene. Diseases associated with FERMT3 include Leukocyte Adhesion Deficiency, Type Iii and Leukocyte Adhesion Deficiency. Among its related pathways are Adhesion and Response to elevated platelet cytosolic Ca2+. GO annotations related to this gene include integrin binding. An important paralog of this gene is FERMT1.

Plays a central role in cell adhesion in hematopoietic cells (PubMed:19234463, PubMed:26359933). Acts by activating the integrin beta-1-3 (ITGB1, ITGB2 and ITGB3) (By similarity). Required for integrin-mediated platelet adhesion and leukocyte adhesion to endothelial cells (PubMed:19234460). Required for activation of integrin beta-2 (ITGB2) in polymorphonuclear granulocytes (PMNs) (By similarity).

Isoform 2 may act as a repressor of NF-kappa-B and apoptosis.

### GO enrichment

