Altered interactions between unicellular and multicellular genes drive hallmarks of transformationin a diverse range of solid tumors

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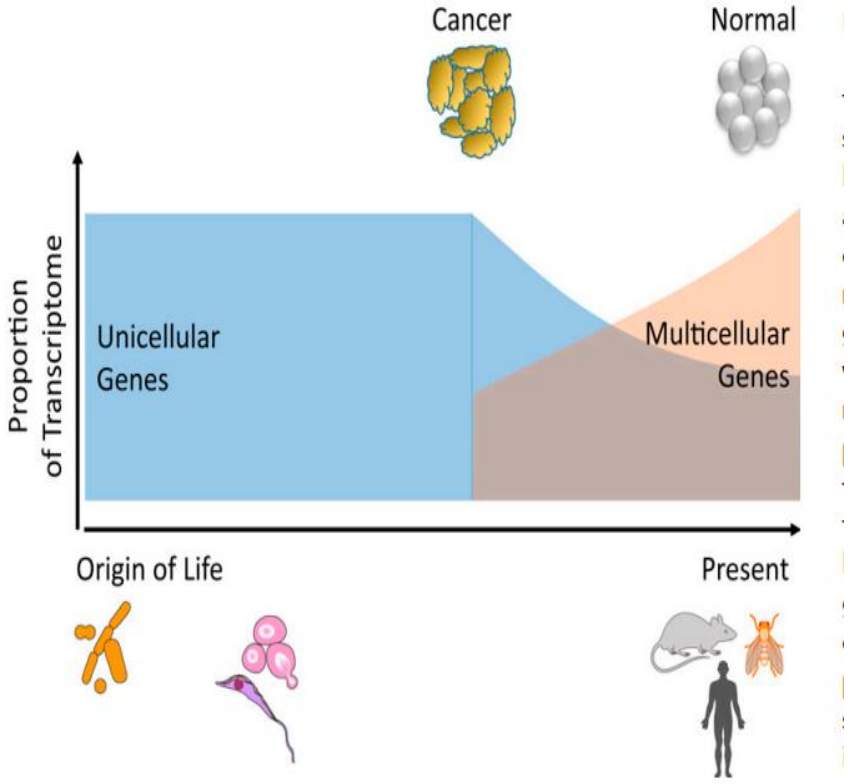
COMMENTARY： *Ancestral gene regulatory networks drive cancer*

较正常细胞而言，癌细胞中来自单细胞的转录酶的比例较高。

“返祖现象”假设癌细胞是因为退化成为像单细胞一样的最原始微生物，因此才会不断分化，无限增殖

癌细胞是单细胞区域中基因的过表达和多细胞区域的基因的欠表达的共同作用



Cancer; 无限分裂，持续扩散、破坏正常组织

Atavistic theory; 返祖的遗传现象是指人类的个体身上出现了人类祖先具有而现代人身上已消失了的解剖生理特征，所以返祖现象也是生物进化的一种证据。

Unicellular &Multicellular ; 单细胞生物只由单个细胞组成，多细胞是由多个细胞共同分化表达的结果。

生物学问题：

在生物体中单细胞基因与多细胞基因的相互作用的层面上，通过对7种不同类型的癌细胞的和正常细胞研究对比，发现其在细胞中表达或相互作用具有很大的差异。本实验通过实验数据印证这些差异，并阐述细胞现象“返祖现象”是作为肿瘤形成的途径。

解决方案:

系统发育学与RNA-seq数据的相结合，通过数据分析，再进行差异性表达分析和相互作用及共表达网络的构建。

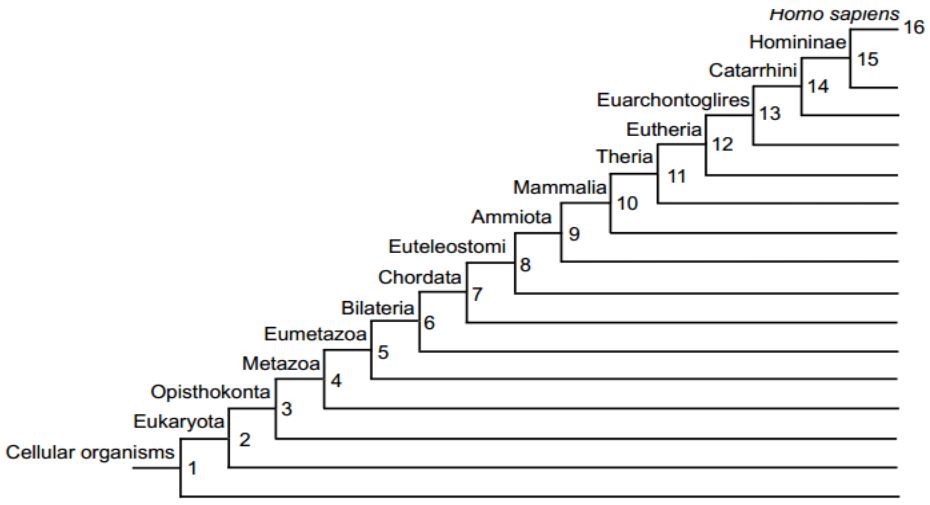


Figure S1. Phylogenetic tree of the 16 phylostrata used in this study.

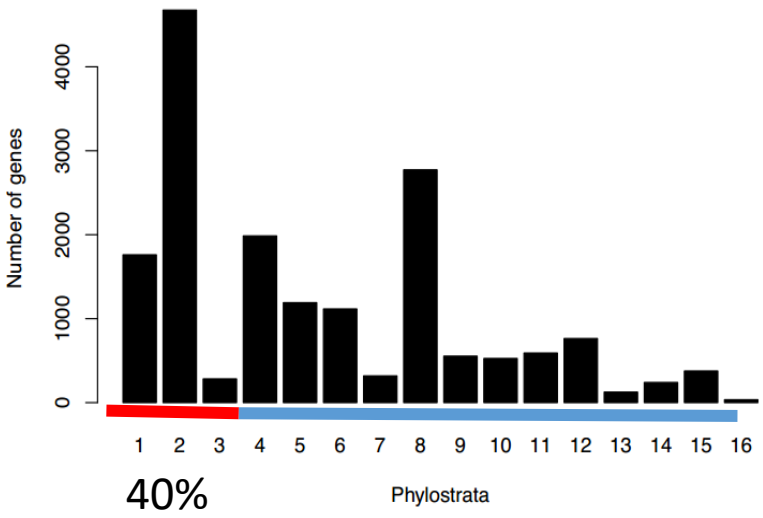


Figure S2. Number of human genes (Ensembl release 7.29) per phylostratum based on phylostratigraphic analysis using OrthoMCL.

通过数据库对已经发现的17,318 human genes 被划分为16个进化枝（clades），划分依据基于“亲缘关系遥远的物种，其直系同源更为明确”

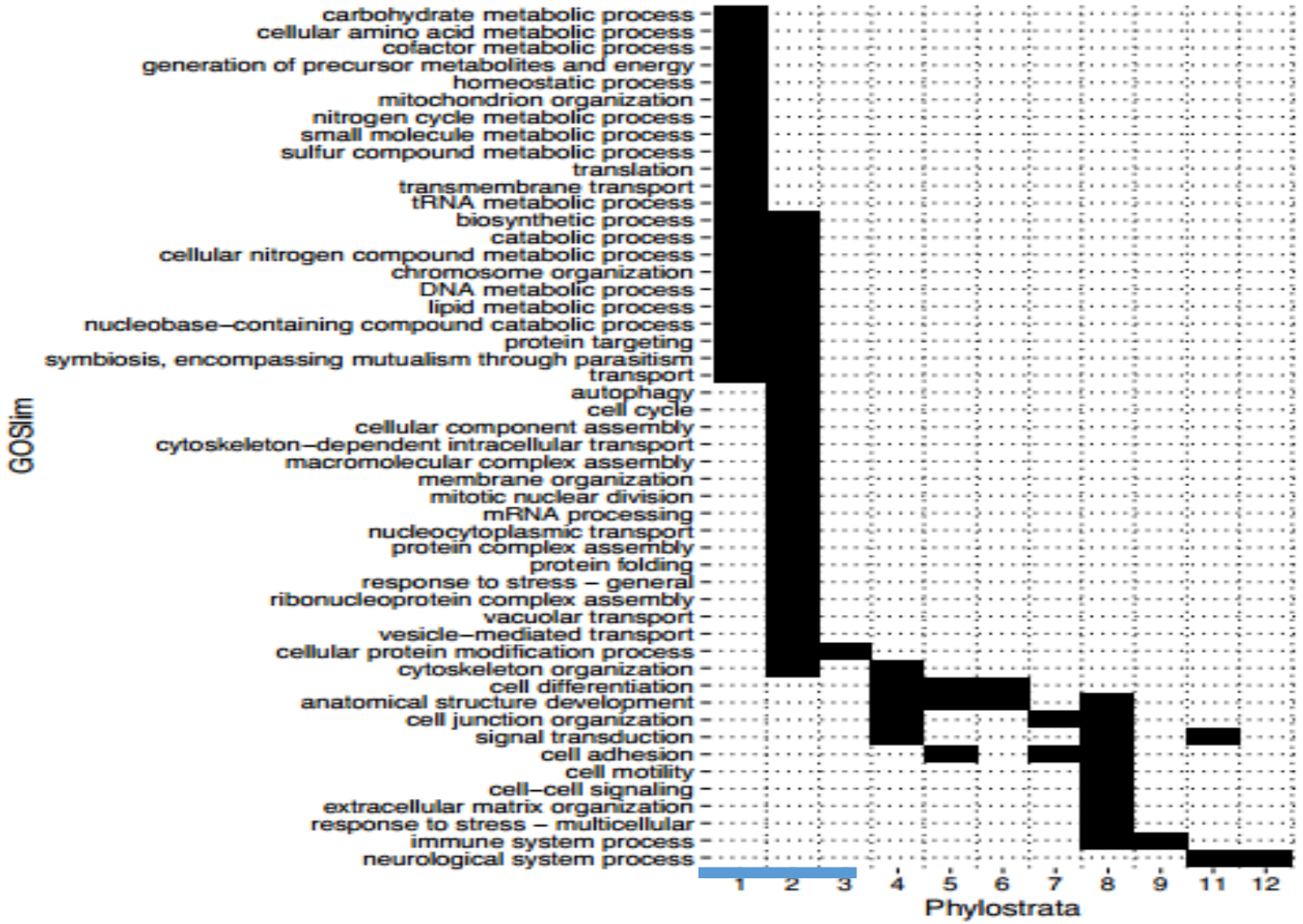


Figure S3. Enrichment of GOslims by phylostratum.

Unicellular ancestors are enriched for basic cellular functions,while multicellular aassociated with complex functions

Purpose:

In order to investigate how the expression of genes in tumors is related to their evolutionary origins

Using RNA-seq gene expression from seven tumor types from TCGA to calculated the transcriptome age index (TAI)

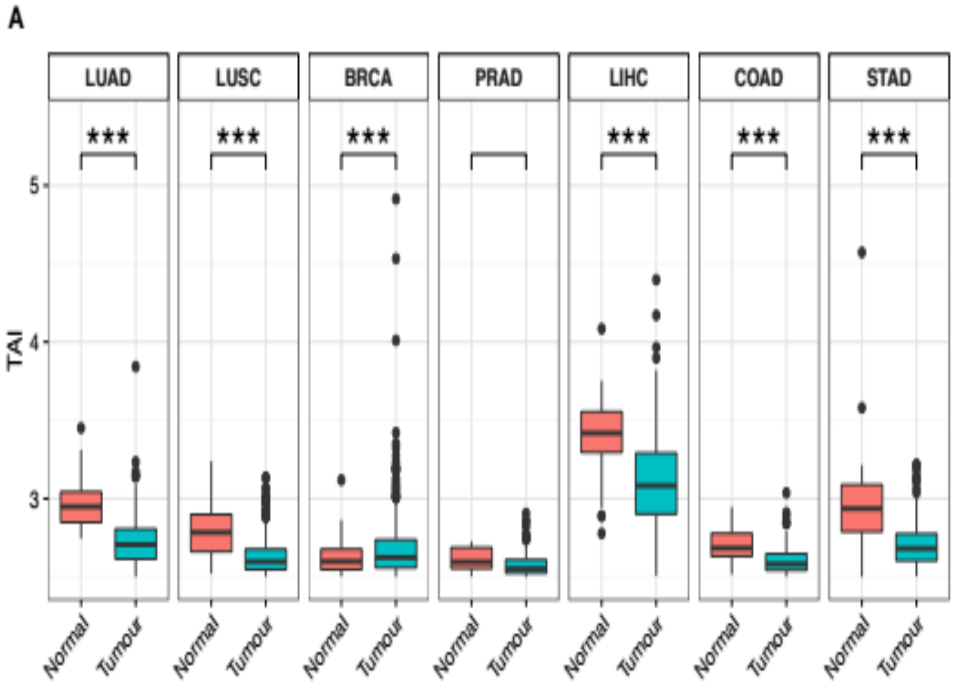
Data Sources:

Seven tumor types from TCGA: LUAD、 LUSC、 BRCA、 PRAD、 LIHC、 COAD、 STAD

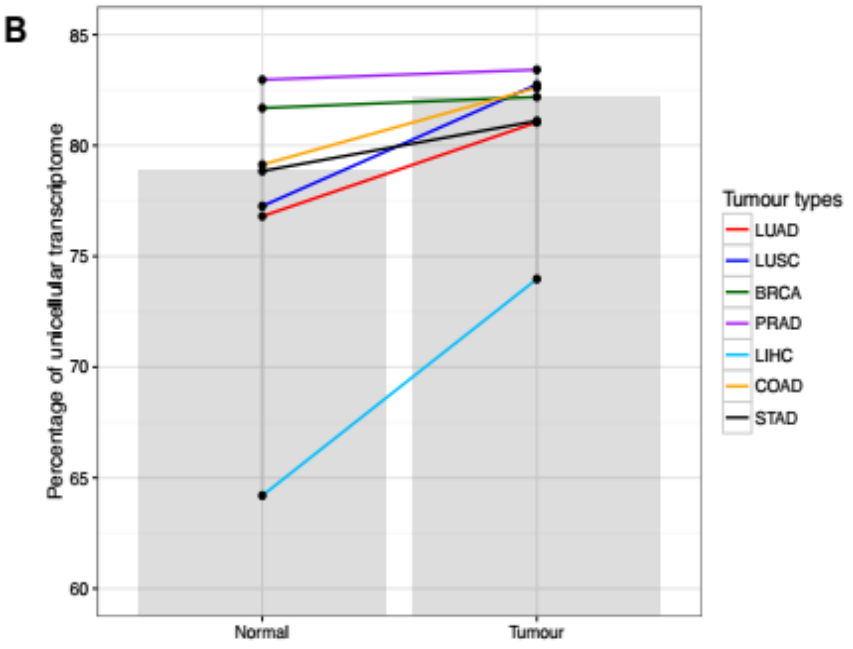
3,473 tumor samples & 386 normal tissue

Transcriptome age index (TAI):

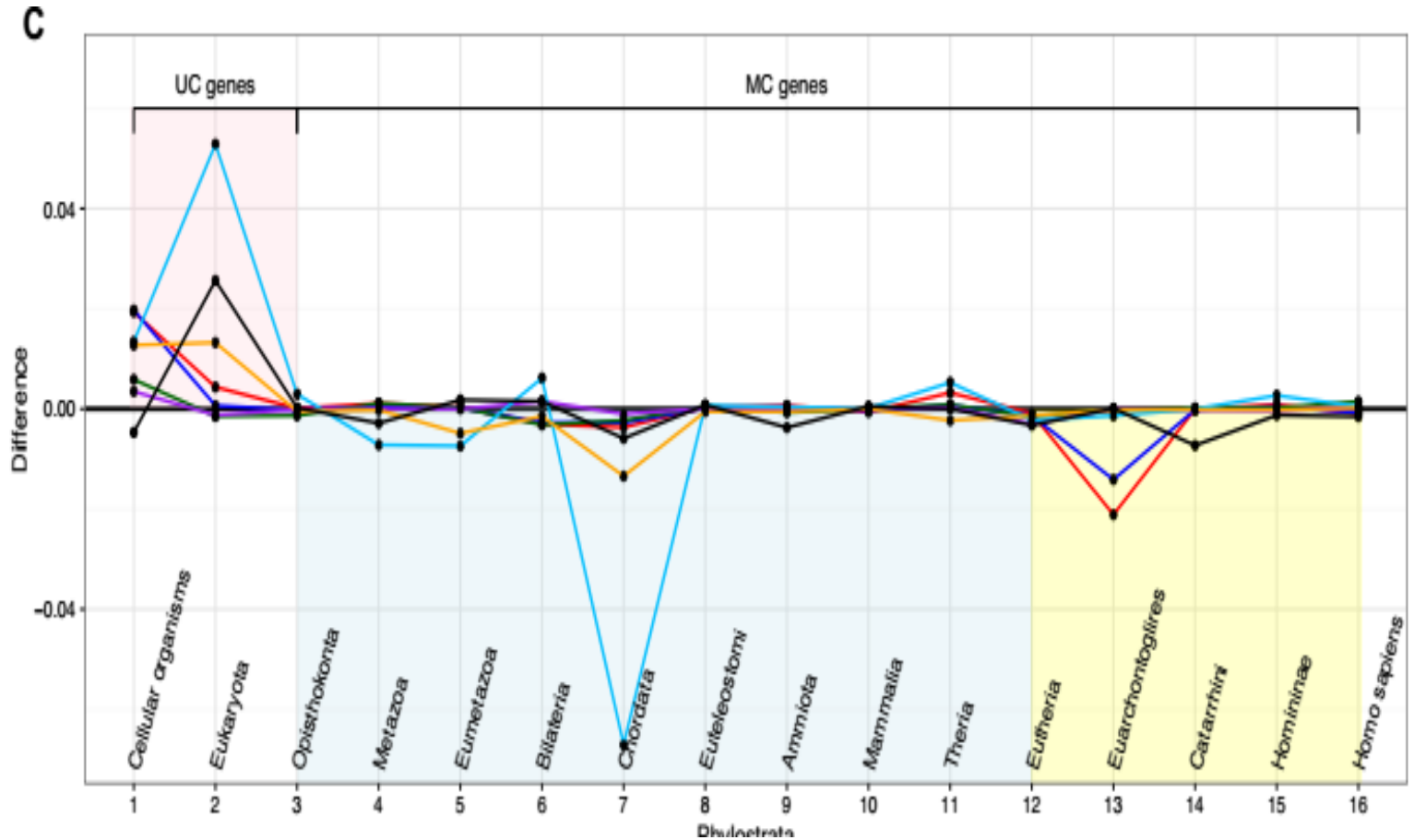
TAI值越低，ancient genes 表达量越高，转录酶越“原始”



Transcriptom Age Index



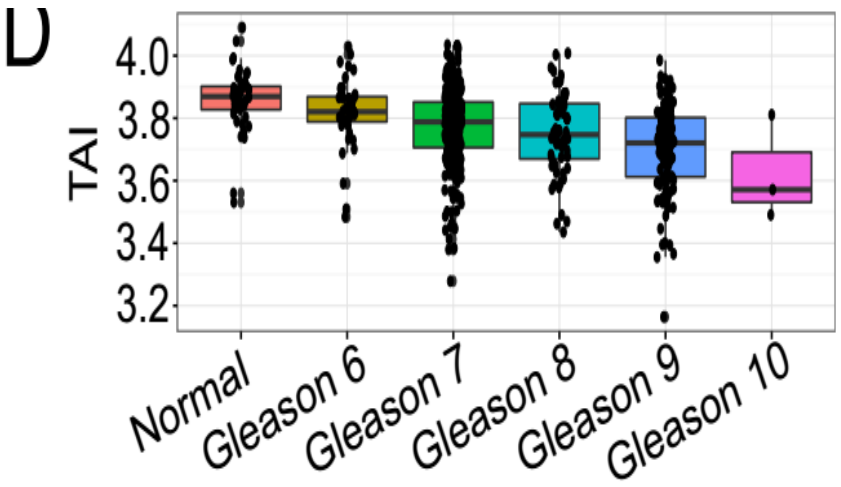
Transcriptome comprised of **unicellular genes**

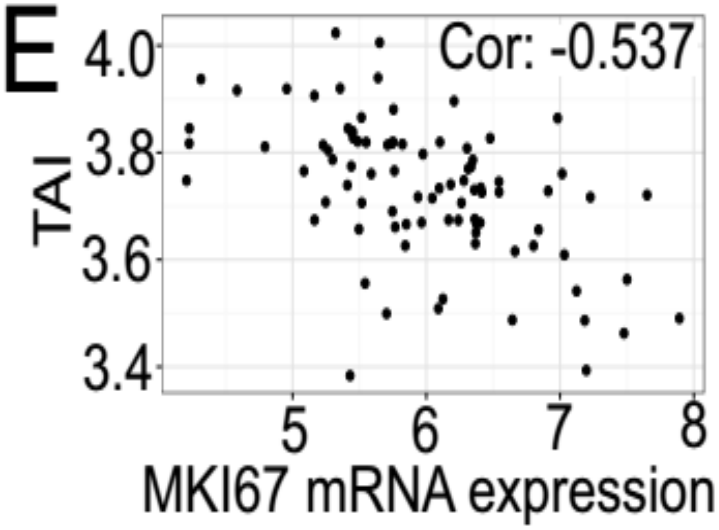


Up-regulated Down-regulated Little difference

Purpose:Investigate the association between the preferential(偏好性) expression of unicellular genes in tumors and clinical features

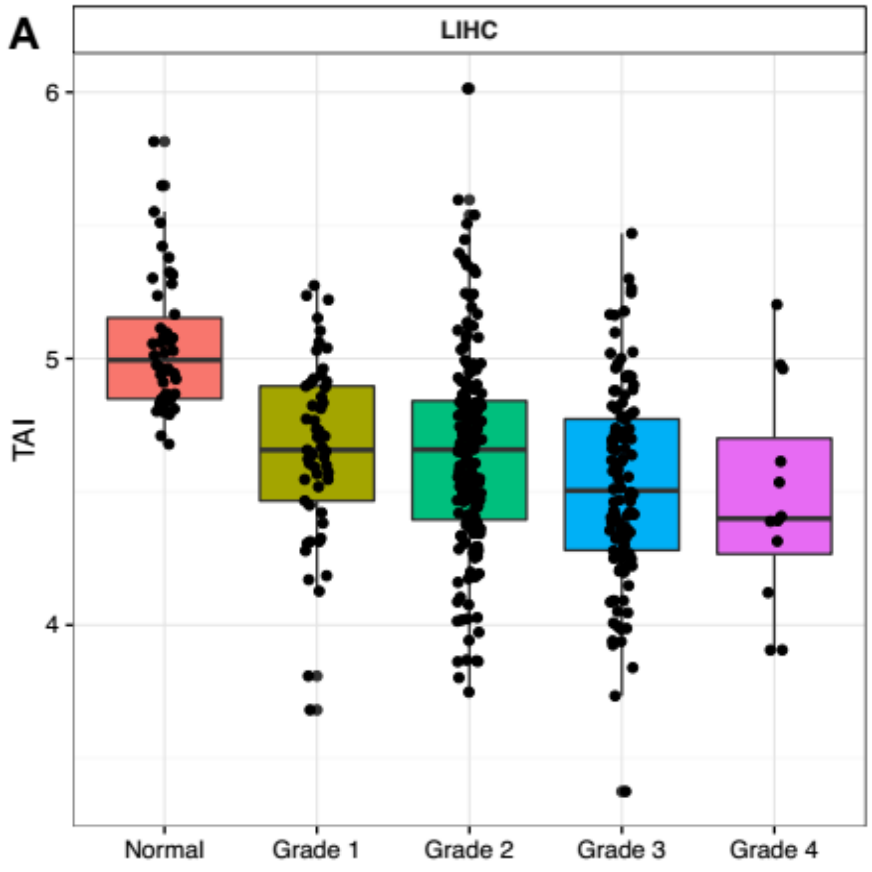
Method :Stratified PRAD（前列腺癌症） samples by Gleason score（癌组织分级的方法，Gleason级越高，细胞分化程度低，癌症越恶劣）

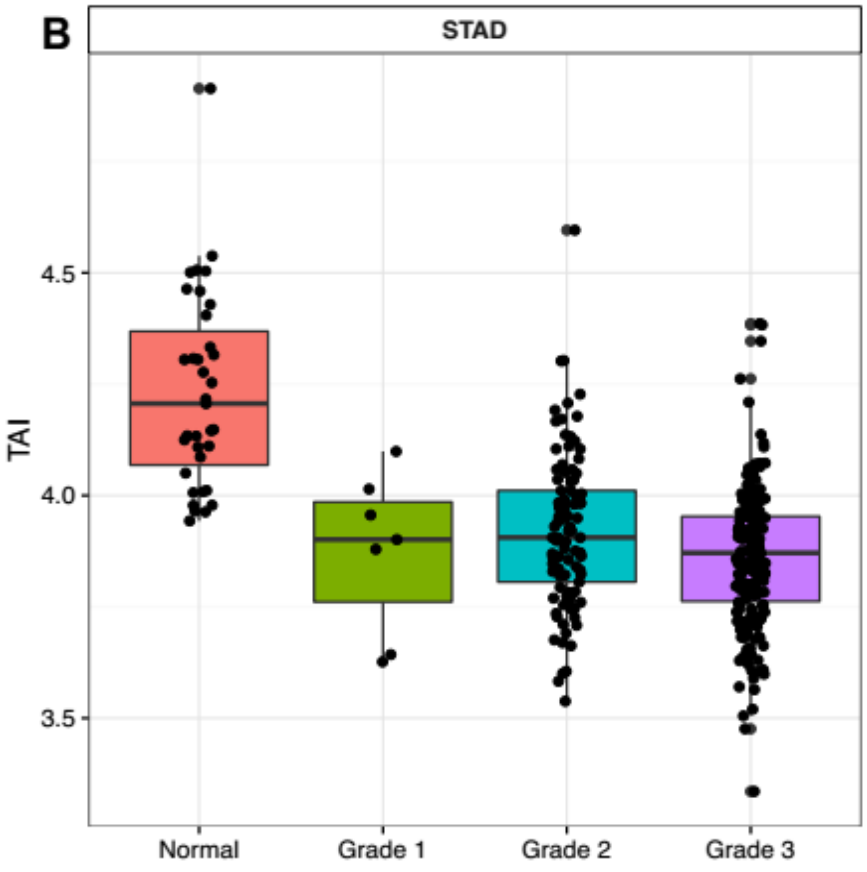




6 to 10 with increasing dedifferentiation

Negative correlation between the MK167 and TAI



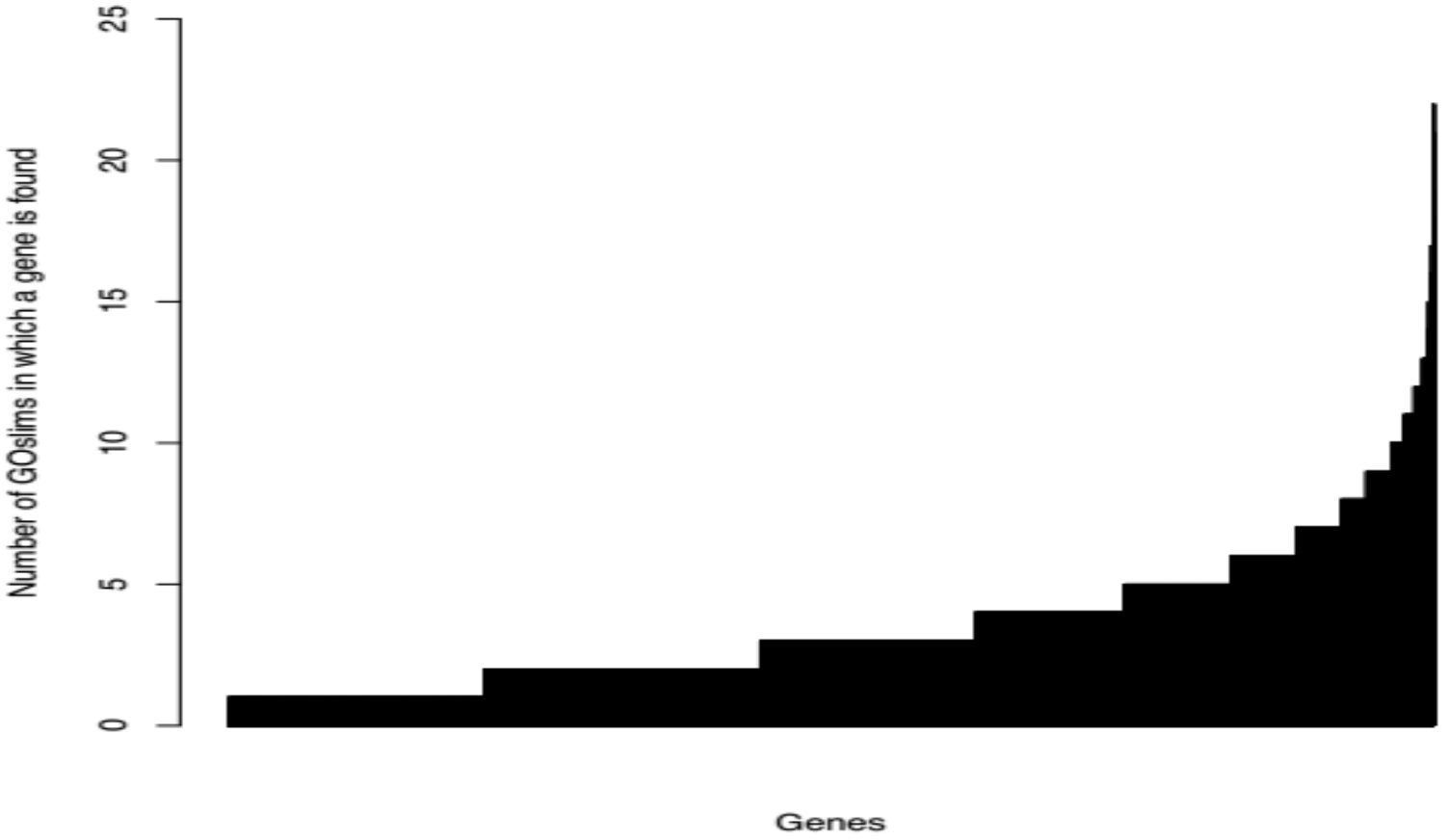


Liver hepatocellular carcinoma

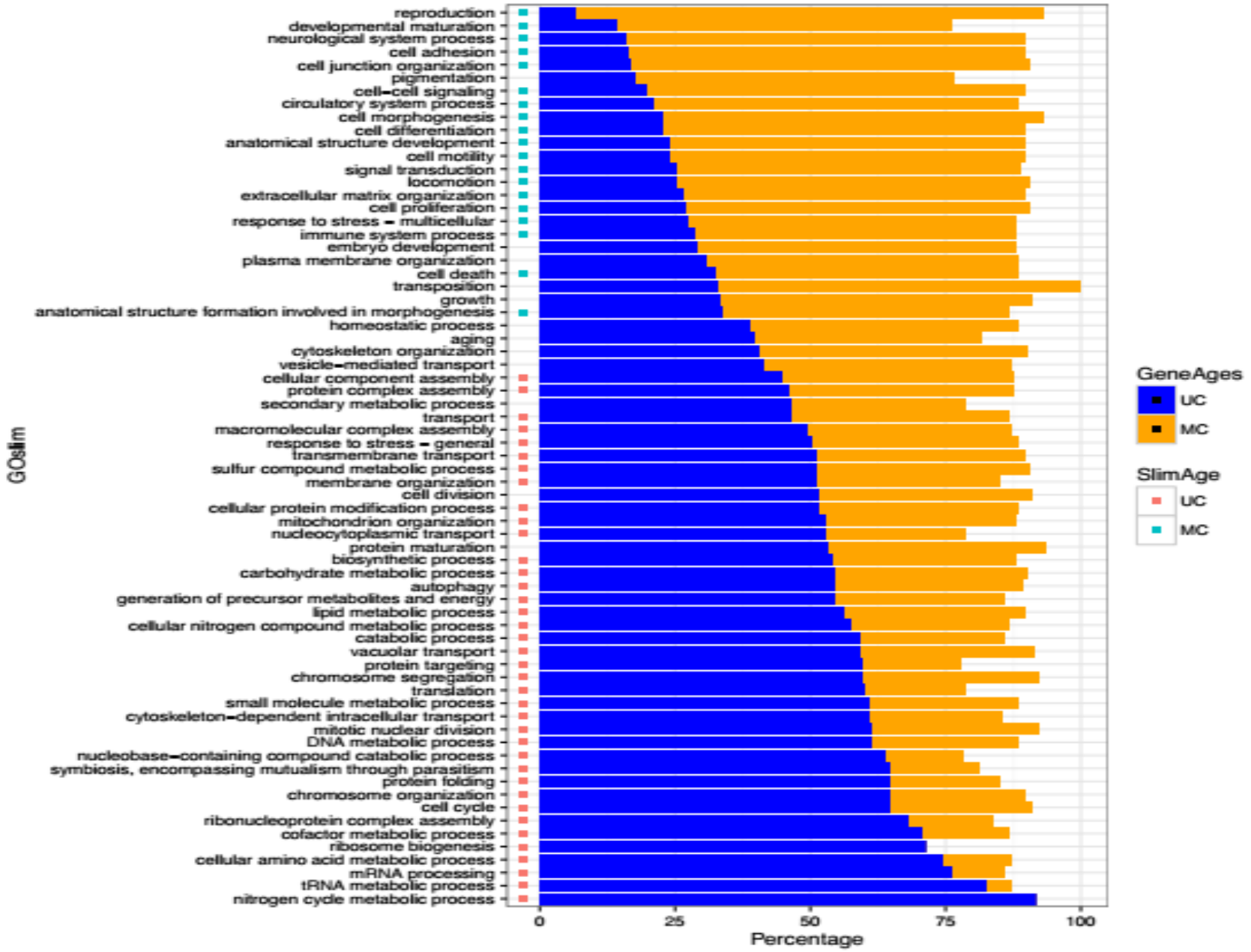
stomach adenocarcinoma

Purpose: Examine the functional of UC genes in tumors

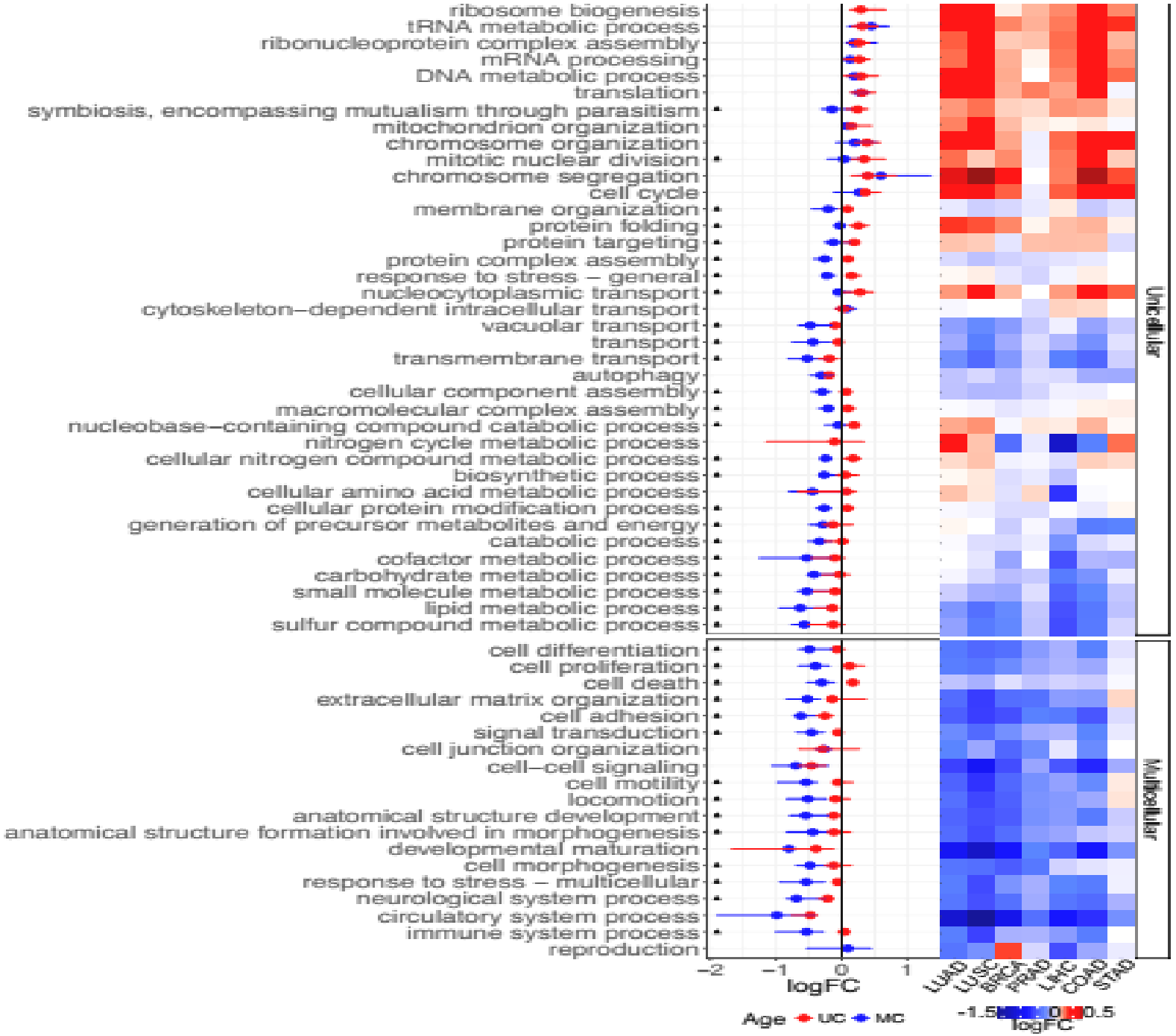
Method: GOslim

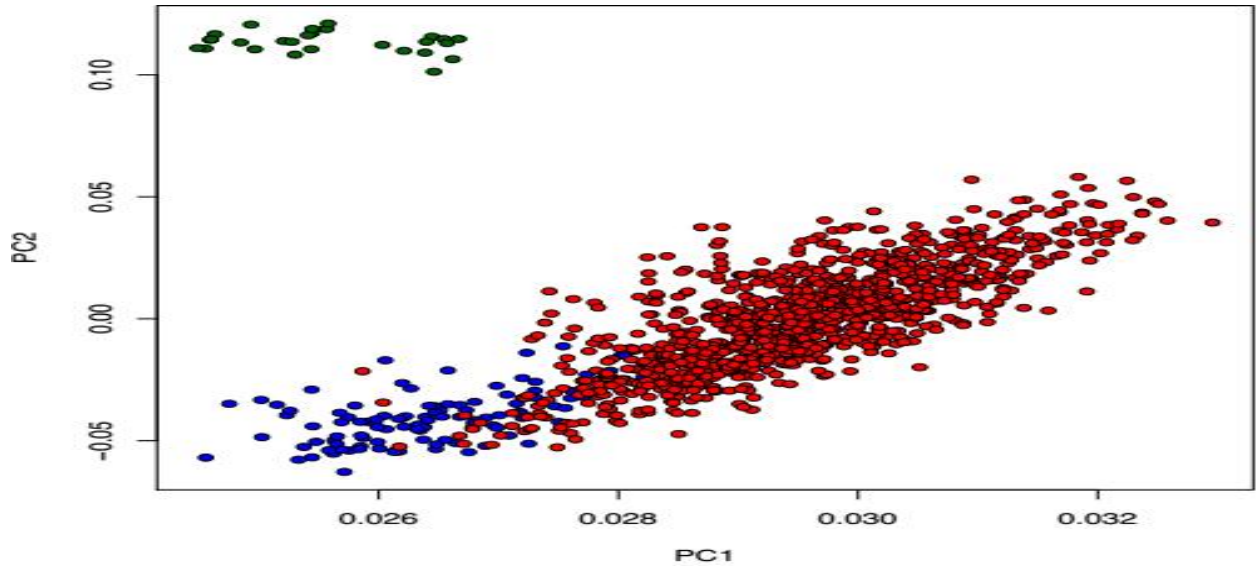


83.21% are annotated to 5 or fewer GOslims

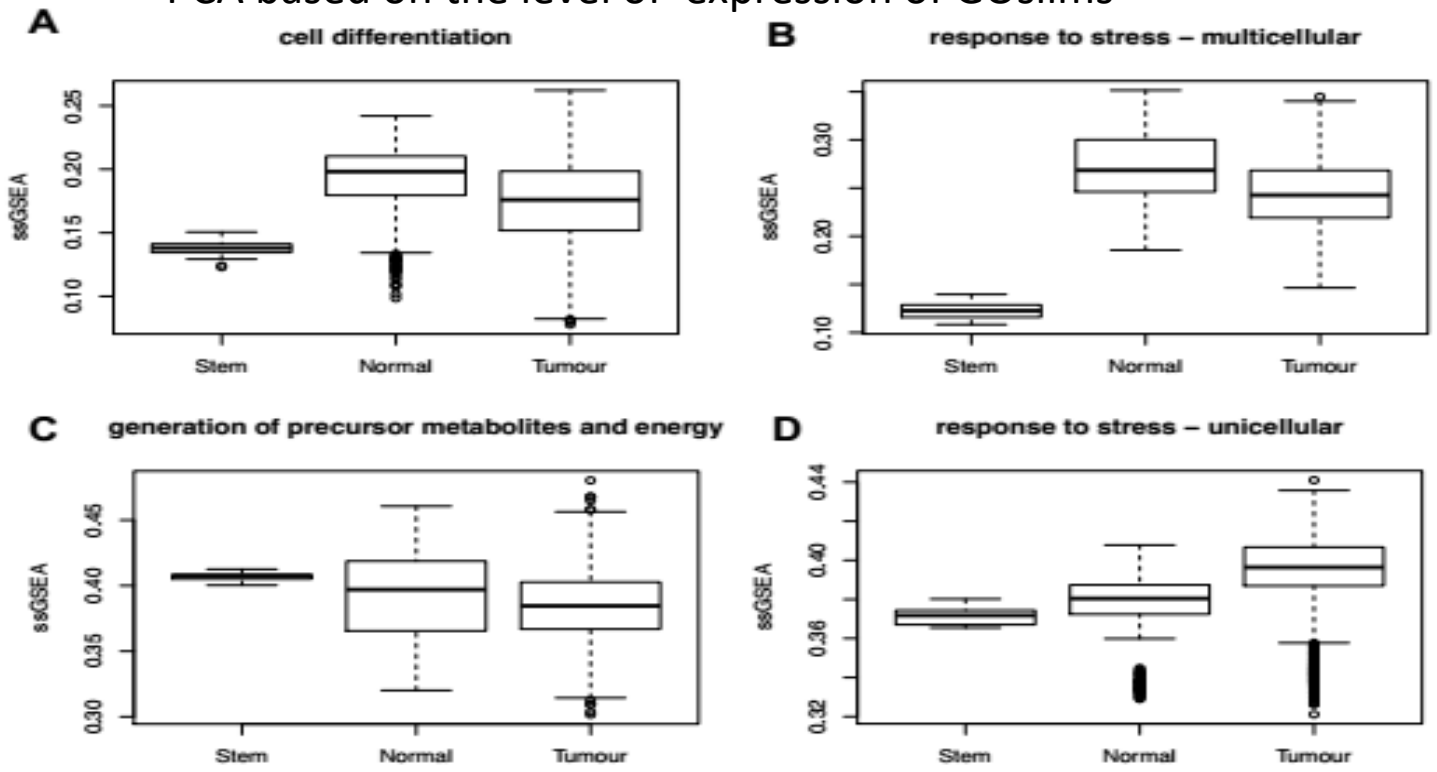


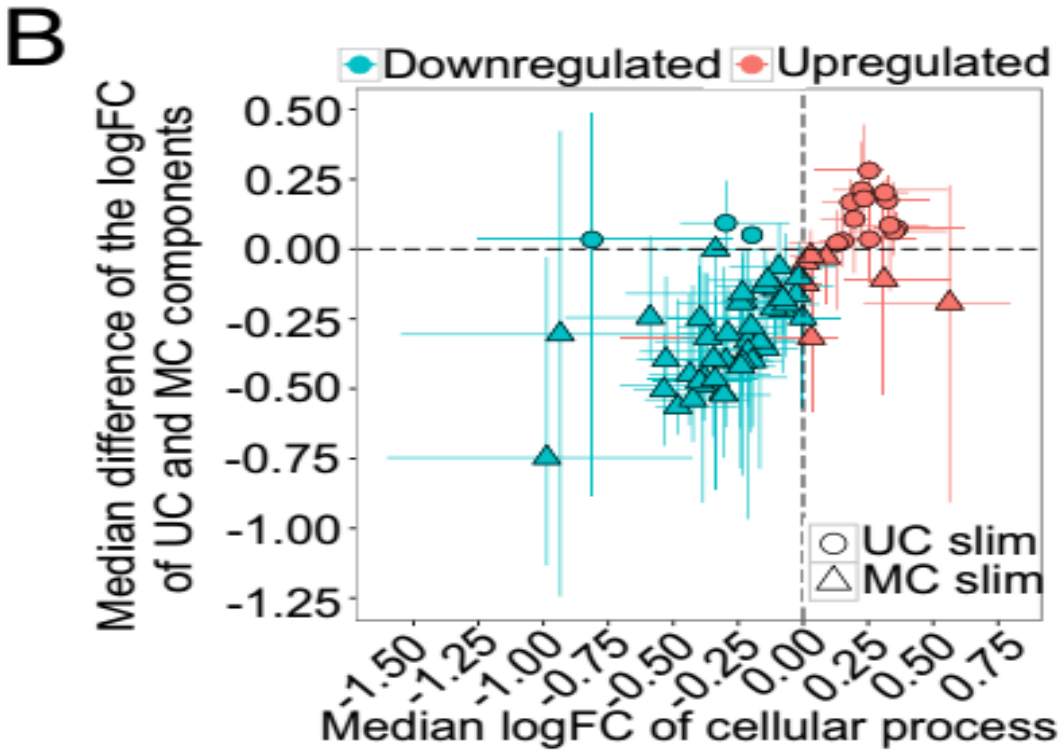
Evolutionary ages of GOslims


ribosome biogenesis
tRNA metabolic process
ribonucleoprotein complex assembly
mRNA processing
DNA metabolic process
translation
symbiosis, encompassing mutualism through parasitism
mitochondrion organization
chromosome organization
mitotic nuclear division
chromosome segregation
cell cycle
membrane organization
protein folding
protein targeting
protein complex assembly
response to stress – general
nucleocytoplasmic transport
cytoskeleton–dependent intracellular transport
vacuolar transport
transport
transmembrane transport
autophagy
cellular component assembly
macromolecular complex assembly
nucleobase–containing compound catabolic process
nitrogen cycle metabolic process
cellular nitrogen compound metabolic process
biosynthetic process
cellular amino acid metabolic process
cellular protein modification process
generation of precursor metabolites and energy
catabolic process
cofactor metabolic process
carbohydrate metabolic process
small molecule metabolic process
lipid metabolic process
sulfur compound metabolic process
cell differentiation
cell proliferation
cell death
extracellular matrix organization
cell adhesion
signal transduction
cell junction organization
cell–cell signaling
cell motility
locomotion
anatomical structure development
anatomical structure formation involved in morphogenesis
developmental maturation
cell morphogenesis
response to stress – multicellular
neurological system process
circulatory system process
immune system process
reproduction
Unicellular
Multicellular
−2
−1
0
1
logFC
LUAD
LUSC
BRCA
PRAD
LIHC
COAD
STAD
Age
UC
MC
-1.5
0
0.5
logFC



PCA based on the level of expression of GOslims

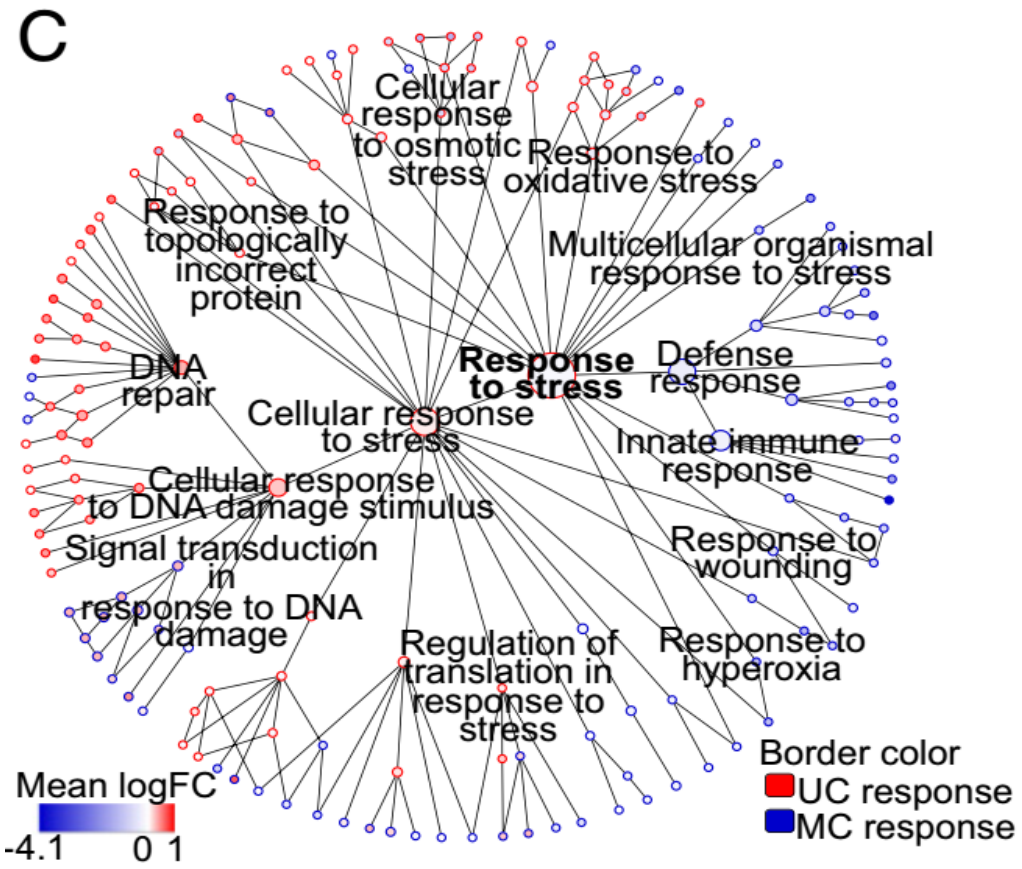




Difference in the absolute logFC of UC and MC components of GOslims (y axis) vs. Overall logFC for the GOslim in tumors vs. normal samples (x axis)

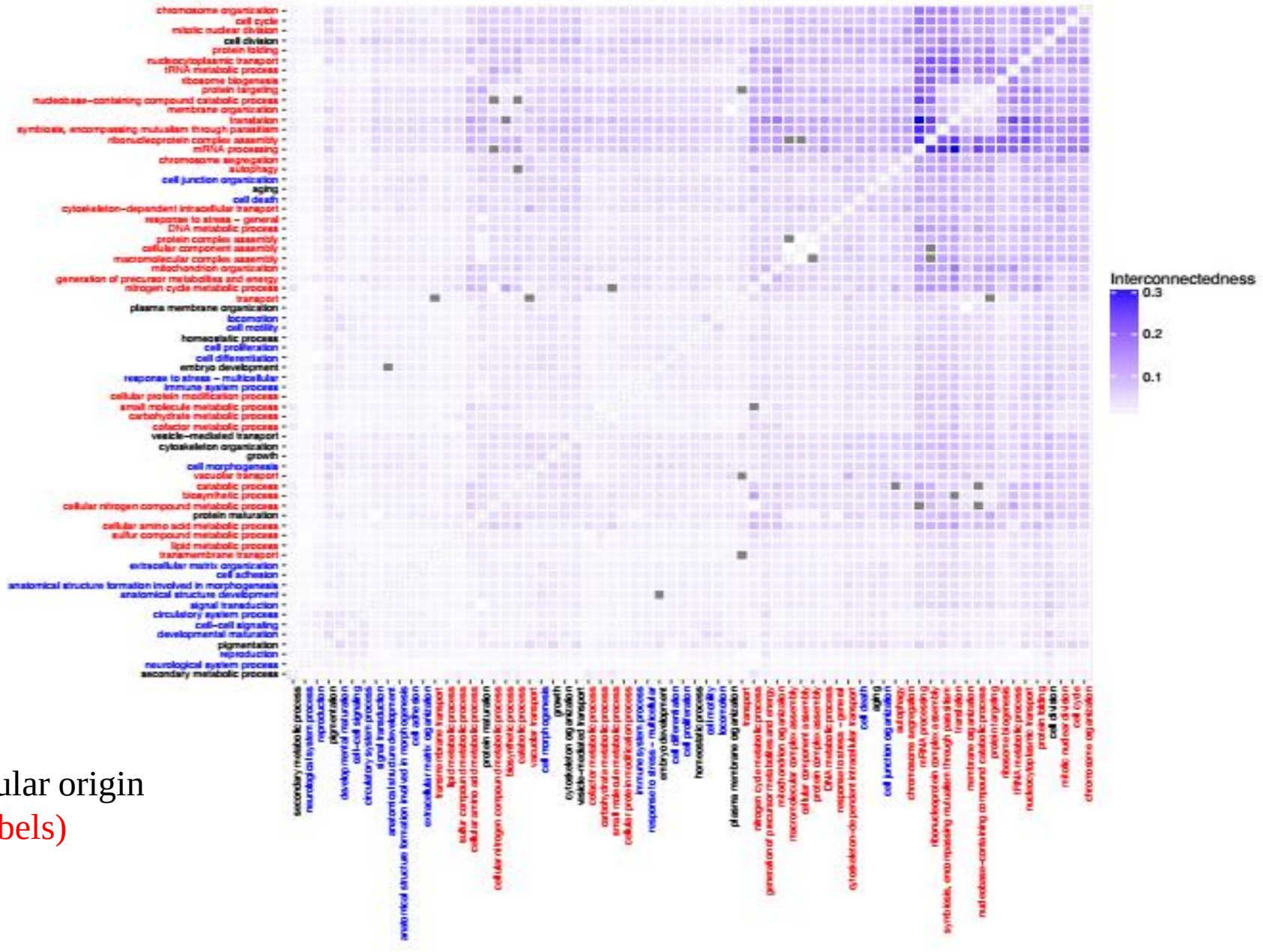
UC Slim upregulated & MC Slim downregulated

Investigated the biological processes that the tumor biology thought to be central to the atavistic process



55% of stress responses conserved with unicellular were up-regulated

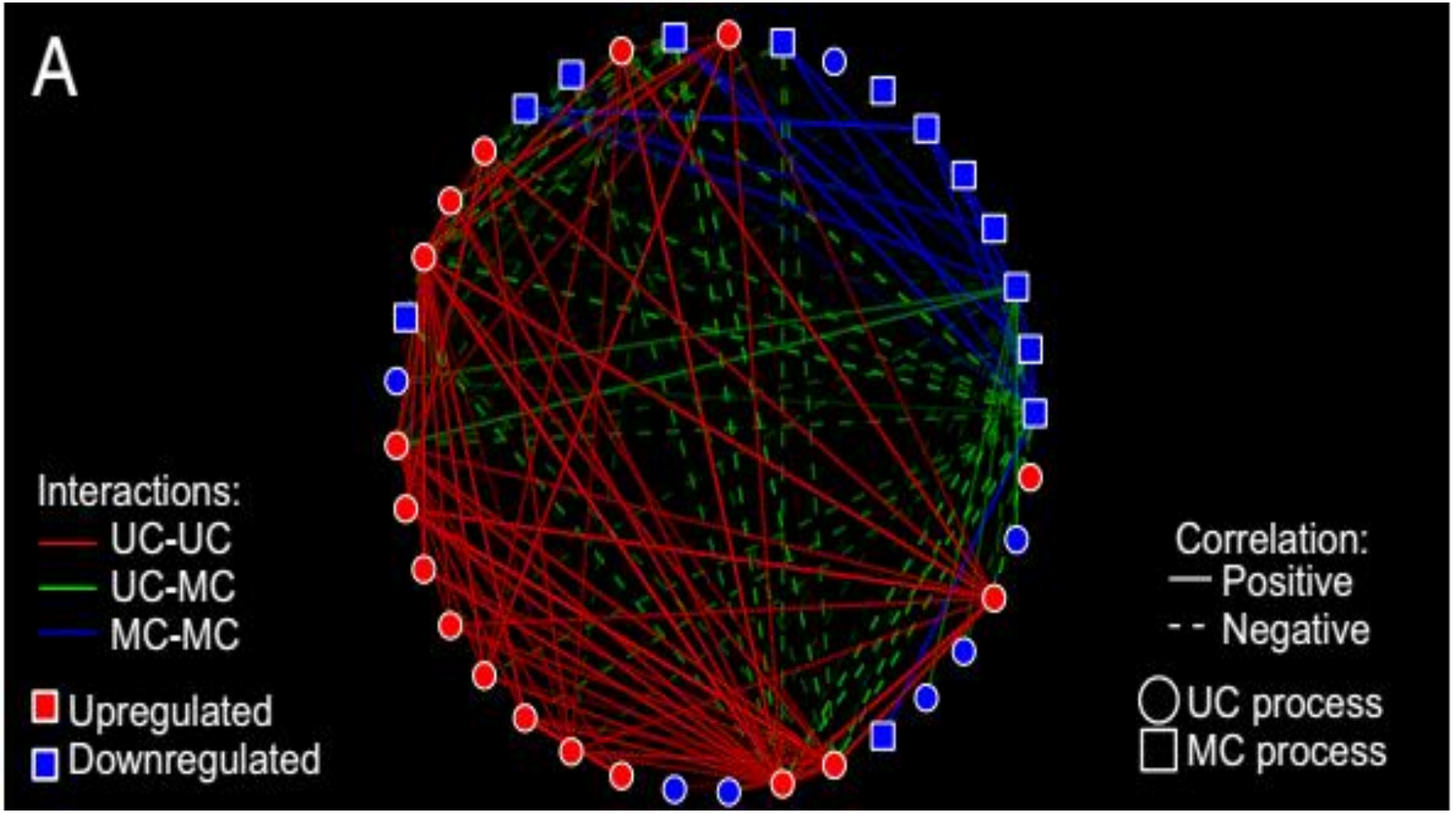
69% of stress responses of multicellular were down-regulated



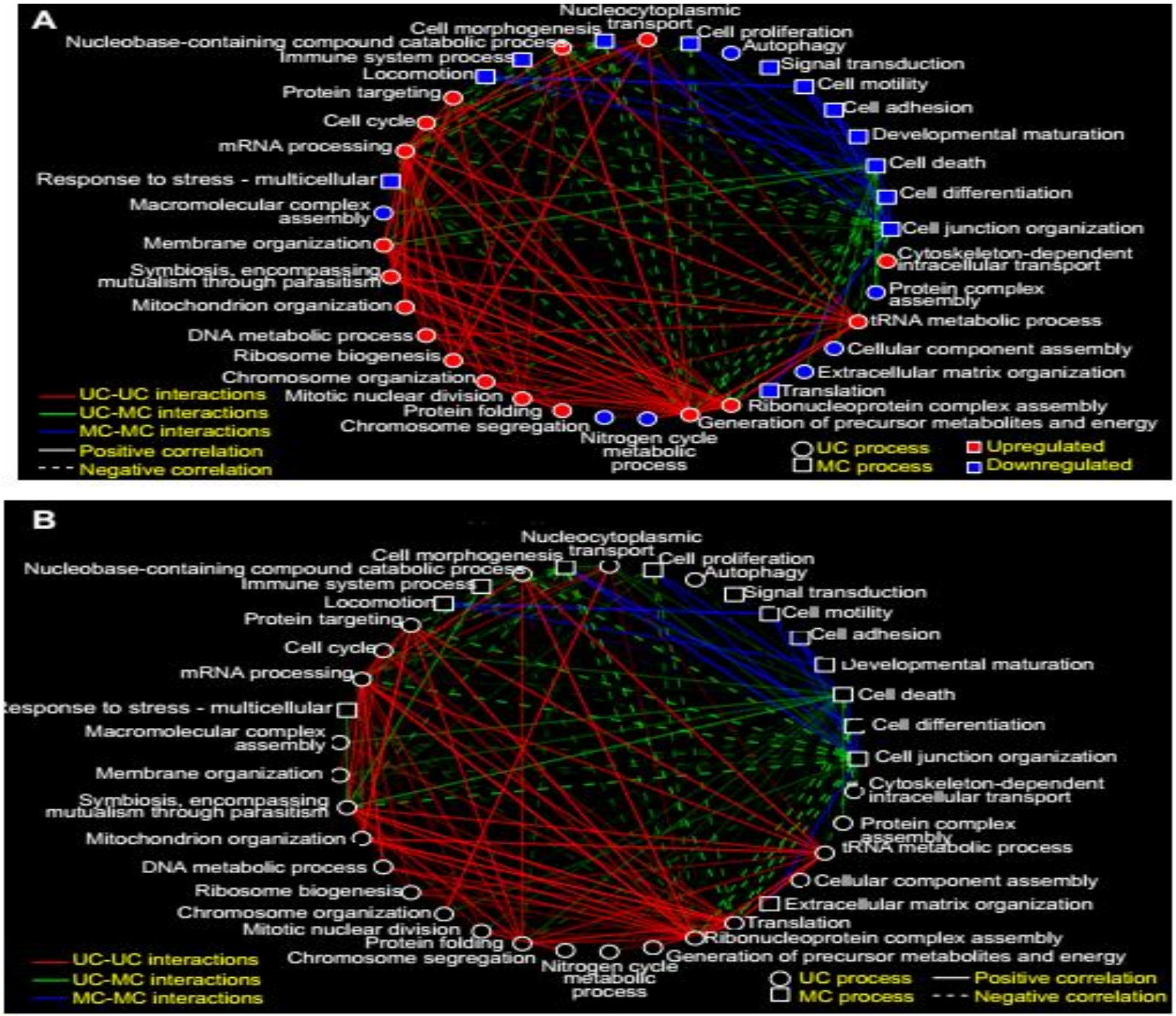
Unicellular origin
(read labels)

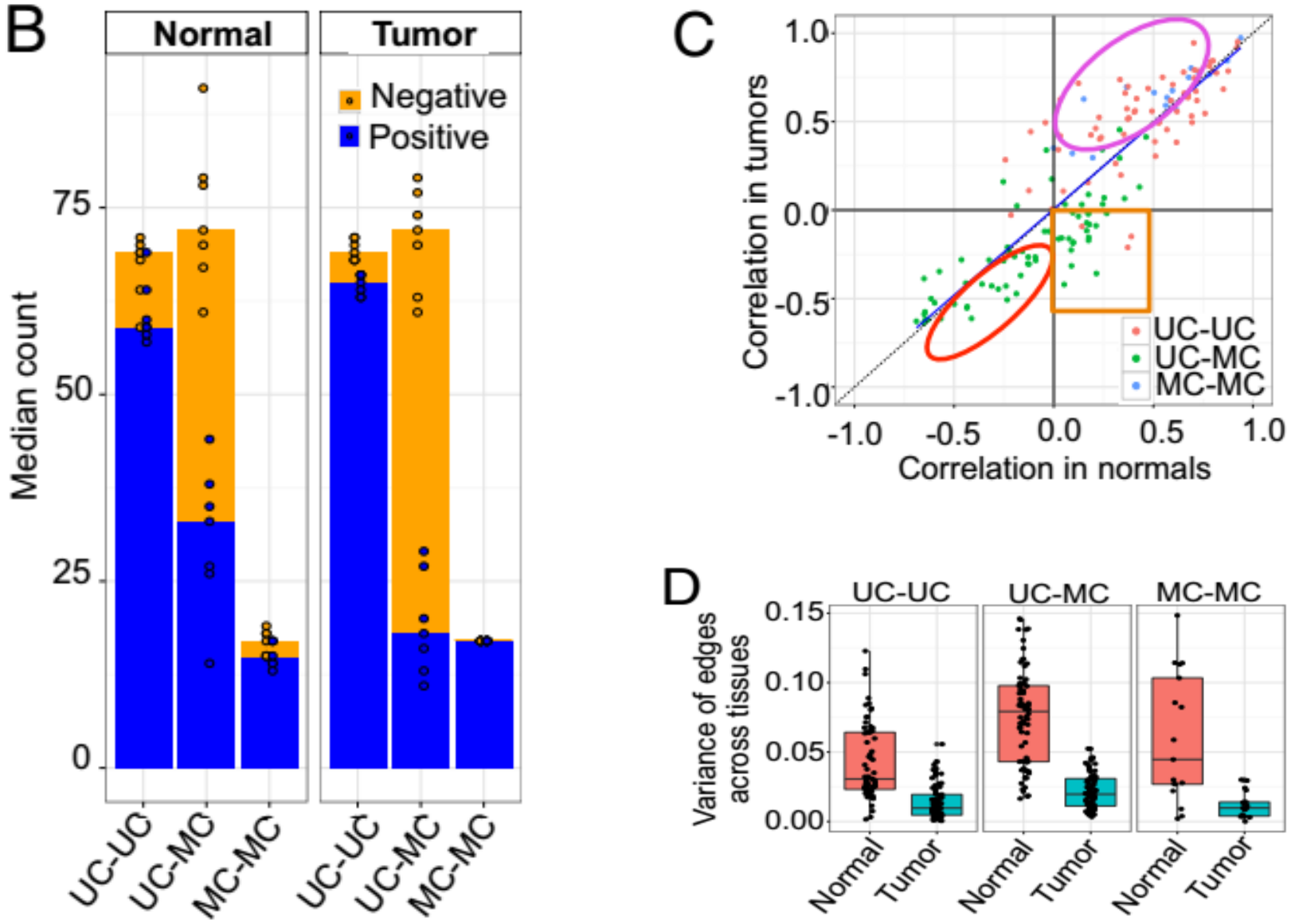
Interconnectedness between cellular processes

Disruption of the Coexpression Between UC and MC Processes in Tumors Enhances Hallmark Phenotypes



Disruption of the Coexpression Between Unicellular and Multicellular Processes in Tumors


A
Nucleocytoplasmic transport
Cell morphogenesis
Cell proliferation
Autophagy
Nucleobase-containing compound catabolic process
Immune system process
Signal transduction
Locomotion
Cell motility
Protein targeting
Cell adhesion
Cell cycle
Developmental maturation
mRNA processing
Cell death
Response to stress - multicellular
Cell differentiation
Macromolecular complex assembly
Cell junction organization
Membrane organization
Cytoskeleton-dependent intracellular transport
Symbiosis, encompassing mutualism through parasitism
Protein complex assembly
Mitochondrion organization
tRNA metabolic process
DNA metabolic process
Cellular component assembly
Ribosome biogenesis
Extracellular matrix organization
Chromosome organization
Translation
Mitotic nuclear division
Ribonucleoprotein complex assembly
Protein folding
Generation of precursor metabolites and energy
Chromosome segregation
Nitrogen cycle metabolic process
UC-UC interactions
UC-MC interactions
MC-MC interactions
Positive correlation
Negative correlation
UC process
MC process
Upregulated
Downregulated
B
Nucleocytoplasmic transport
Cell morphogenesis
Cell proliferation
Autophagy
Nucleobase-containing compound catabolic process
Immune system process
Signal transduction
Locomotion
Cell motility
Protein targeting
Cell adhesion
Cell cycle
Developmental maturation
mRNA processing
Cell death
esponse to stress - multicellular
Cell differentiation
Macromolecular complex assembly
Cell junction organization
Membrane organization
Cytoskeleton-dependent intracellular transport
Symbiosis, encompassing mutualism through parasitism
Protein complex assembly
Mitochondrion organization
tRNA metabolic process
DNA metabolic process
Cellular component assembly
Ribosome biogenesis
Extracellular matrix organization
Chromosome organization
Translation
Mitotic nuclear division
Ribonucleoprotein complex assembly
Protein folding
Generation of precursor metabolites and energy
Chromosome segregation
Nitrogen cycle metabolic process
UC-UC interactions
UC-MC interactions
MC-MC interactions
UC process
MC process
Positive correlation
Negative correlation


B
Normal
Tumor
Negative
Positive
Median count
75
50
25
0
UC-UC
UC-MC
MC-MC
UC-UC
UC-MC
MC-MC
C
Correlation in tumors
1.0
0.5
0.0
-0.5
-1.0
-1.0
-0.5
0.0
0.5
1.0
Correlation in normals
UC-UC
UC-MC
MC-MC
D
Variance of edges across tissues
0.15
0.10
0.05
0.00
UC-UC
UC-MC
MC-MC
Normal
Tumor
Normal
Tumor
Normal
Tumor

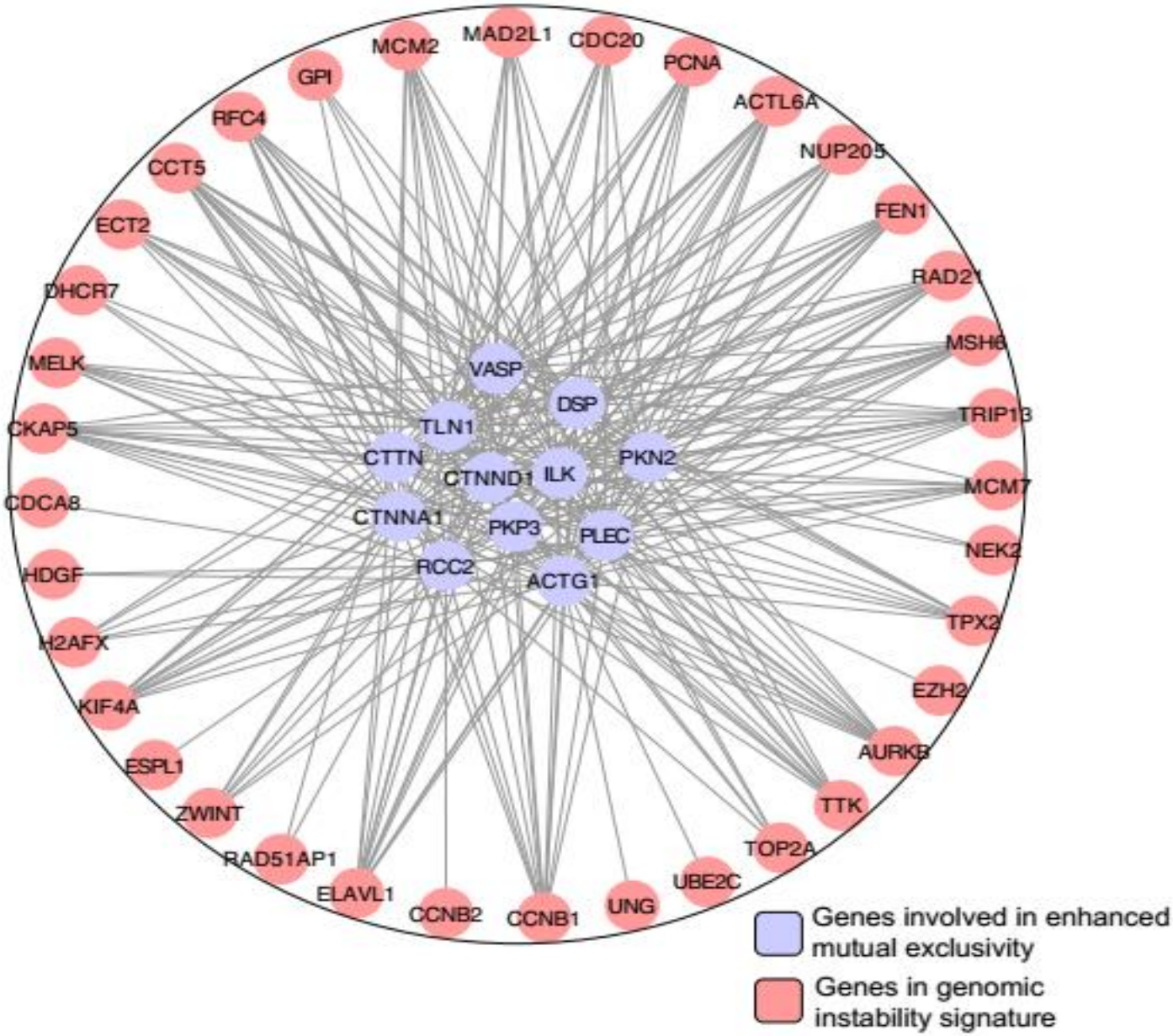


Figure S33. Interactions between key genes of the enhanced mutual exclusivity in tumors with genes associated with genomic instability.

主要结论：

1、在肿瘤中基因的表达发生了的变化且与基因的进化年龄密切相关

2、在肿瘤中单细胞基因的表达上调。多细胞基因表达下调,相对于正常细胞而言

3、肿瘤基因转录过程，在高度保守的基因表达作用更强

4、UM-MC的共表达，对于细胞中的染色体结构和代谢途径有着重要的意义

5、在许多肿瘤中，多细胞和单细胞基因具有较强的共表达能力，寻找到了12个关键基因，其在癌细胞组织和染色体组织之间的共同表达起关键作用

Enlightenment

本篇文献对癌细胞返祖现象的研究，逐步深入，真正提供了分子层面的证据，为以后的癌症的治疗及诊断提供新的思路

对比正常组织细胞和癌细胞中Unicellular和Multicellular，通过差异表达分析，得出了癌细胞中的UC 发挥关键作用，为返祖现象的证明提供了依据。

构建了在癌细胞中的共表达的调节网络，明确了MC-UC的相互作用的改变是细胞癌变的主要影响因素。

进一步确定了12影响个UC-MC的关键基因，进一步揭示了癌细胞分子机理

View

还未对癌症细胞的返祖现象，提供明确的机制或途径，来阐释这整个过程。

影响MC-UC共表达的这12个关键基因，还有很多信息值得挖掘。

请多提宝贵建议

谢谢