Genome-wide views of aging gene networks





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Human Aging Phenotypes Young Old











Individual

Tissue



Genes



Kidney as a model for human aging

- Filtration rate declines with age
- Easy to test function
- 74 samples (age 27-92)



74 donors

Age	Number
<41	4
41-50	10
51-60	16
61-70	13
71-80	20
81-90	10
>90	1

Divide into cortex and medulla sections

Genome-wide scan for gene expression changes

447 age-regulated genes in the human kidney



0

Each row is a gene

Yellow is high level expression Blue is low level expression

Each column corresponds to a person, youngest to oldest

left: Cortex right: medulla

+3

Medulla

-3

Cortex

Age-induced genes

Marker of physiological age?



VS







Molecular profiles reveal Physiological Age?

Medulla



Cortex

- Measure kidney function and appearance "biological age"
- See if genes correlate • with time or appearance of kidney

Normal



Glomerulosclerosis (0-4)

arterial intimal hyalinosis (0-4)



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Normal

• 2002 Elever Listed All rights reserved. tubular atrophy and²⁰⁰³ Elever Listed All rights reserved. interstitial fibrosis (0-4)



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Combine into chronicity index (0-12)

patient 40 (29 years old with a chronicity score of 0)

patient 62 (84 years old with a chronicity score of 10)





Gene expression profiles predict kidney physiology





Transcriptional profiling of the aging mouse (data from AGEMAP consortium)

C57BL/6 Mice

1, 6, 16, and 24 months

5 male/5 female per age point



Mouse 17K A/B arrays

-

Mouse Tissues

Adrenal Glands Kidney Bone Marrow Liver Cerebellum Lung Cerebrum **Muscle Spinal Cord** Eye Gonads Spleen Heart Striatum Hippocampus Thymus

617 gene arrays total

346 Thymus genes change expression levels with age



Varying amounts of age-regulation in different tissues



Nine tissues exhibit significant age-regulation in the mouse



Do tissues in the mouse age similarly?



11 tissue pairs share common patterns of aging

Tissues ^a	Adrenals ^b	Cerebellum	Eye	Gonads	Heart	Lung	Spleen	Spinal Cord	
Cerebellum	> 0.05							° 	
Eye	> 0.05	> 0.05							
Gonads	10 ⁻⁴	> 0.05	> 0.05						
Heart	0.042	> 0.05	10 ⁻¹²	> 0.05				s 	
Lung	0.047	> 0.05	> 0.05	0.027	10 ⁻⁹				
Spleen	> 0.05	> 0.05	> 0.05	> 0.05	0.0125	10 ⁻²¹			
Spinal Cord	> 0.05	10 ⁻⁶	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	>	
Thymus	10 ⁻⁴	> 0.05	> 0.05	10 ⁻³⁶	> 0.05	> 0.05	> 0.05	> 0.05	

^a Fisher's exact test of independence on age-regulated genes (p < 0.01) for all two tissue pairings

^b *p*-values for Fisher's exact tests of independence

Three patterns of mouse tissue aging



Vascular: Heart, Spleen, Lung

Glandular:

Thymus, Gonads, Adrenals

Neural: Cerebellum, Spinal Cord



Similarity in aging in different species?



Lund et el., 2001



Pletcher et al., 2000



K. Becker, unpub. data.



Gene Set Enrichment Analysis



- Entire pathways more sensitive than single genes
- Assay 624 gene sets (10-200 genes)
- Use van der Waerden statistic to determine which pathways are coordinately changing with age

22 gene sets are commonly ageregulated in human and mouse



A public age-regulated pathway



Human p<	Mouse <i>p</i> <	Fly <i>p</i> <	Worm <i>p</i> <			
0.01	0.02	0.001	0.001			

Reactive Oxygen and the Electron Transport Chain



Comparison of aging at the global level



Human and mouse show no global aging similarity





8932 genes

-3

3

16 tissues



 8932×8932 correlation differences

Clusters That Change With Age

6 months





16 months



24 months



Correlation Difference: Method

1) Create correlation matrix from expression data for older (24 months) and younger (16 months) mice

	1 Expt	Expt 2	Expt 3	Expt		,	Gene 1	Gene 2	Gene 3	Gene 4	Gene 5	Gene 6
Gene 1	.22	.14		.12	Snearman	Gene 1	1.000	0.059	-0.990	-1.000	1.000	-0.310
Gene 2	.05	.21	.3	05	Spearman	Gene 2		1.000	0.025	-0.725	-0.215	-0.865
Gene 3	23	.12	10	.24	acmalations	Gene 3			1.000	-0.387	0.099	0.294
Gene 4	.13	.14	.02	-	correlations	Gene 4				1.000	1.000	-0.011
Gene 5	-	03	- 14	- 06		Gene 5					1.000	-0.196
Gana 6	02	16		2		Gene 6						1.000
Gene	.02	10	08	.3								

2) Use fisher transformation to normalize correlations

$$t = 0.5 \log \frac{1+r}{1-r}$$



3) Subtract (young - old) correlations



Correlation differences with age



Higher in young

Higher in old

More clusters have decreased correlation with age than



Cluster examples:

Cluster enriched in electron transport genes (cluster 84):





22



Cluster enriched in both telomere maintenance and DNA damage repair genes (cluster 99):



Identifying Tissue Specific Effects in Loss of Correlation

- $r_1 r_2 = \sum (d_{1i}^2 d_{2i}^2)$
- For each experiment you can calculate that experiments contribution to the difference in correlation (d_{1i}² - d_{2i}²)



Identifying Tissue Specific Effects in Correlation Loss

• Ex: cluster with enrichment for nerve ensheathment genes:





Molecular markers of human



aging





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