

Supplementary Figure 1. Transcriptional signatures of aging in the kidney and liver.

(a, b) Volcano plot showing aging-associated genes in kidney (a) and liver (b). Blue dots represent aging-associated downregulated genes, and red dots represent aging-associated upregulated genes. And selected typical inflammation and metabolism related genes are labeled.

(c, d) Biological process GO analysis based on commonly significantly changed genes in kidney and liver. Top 5 most significantly enriched terms in commonly upregulated genes (c) and downregulated genes (d) are shown.

	D						
	GSEA of inflammation related pathways	SEA of metabolism related pathways					
Kidney	Liver	Kidney	Liver		<-3 -2 -1 0	1 2 >3	
	Tnf superfamily cytokine production			Peroxisome	Significant score	e (-logPvalue)	
	II6 jak stat3 signaling			Butanoate metabolism			
	Interferon gamma response			Saturated fatty acids β-ox	idation		
	Cell activation involved in immune response			Metabolic pathways			
	Positive regulation of the superfamily cytokine production			Oxidative phosphorylation	cille degradation		
	Allograft rejection			Citrate cvcle			
	Inflammatory response			Pyruvate metabolism			
	Regulation of neuroinflammatory response			TCA cycle			
	Leukocyte activation involved in inflammatory response			Ubiquitin mediated proteo	lysis		
	Regulation of inflammatory response			Porphyrin and chlorophyll metabolism Superpathway of methionine degradation			
	Tnfa signaling via nfkb						
	Inf gamma production			Propanoate metabolism			
	li6 production			Glycine serine and threen	ine metabolism		
	Nfkb signaling pathway			Bile secretion	ine metabolism		
	Inflammatory response to antigenic stimulus			Trihvdroxycoprostanovl C	OA β oxidation		
	Natural killer cell mediated cytotoxicity			Biosynthesis of unsaturafa	atty acids		
	Antigen processing and presentation			Nicotine degradation	,		
	Autoimmune thyroid disease			Tryptophan metabolism			
	Neuroinflammatory response			Tyrosine metabolism			
	Interferon alpha response			Ascorbate and aldarate m	etabolism		
	Response to interferon gamma			Phytanic acid peroxisoma	I oxidation		
	Positive regulation of interleukin 6 production			Pentose and glucuronate	interconversions		
	Nod-like receptor signaling pathway			Omega-6 fatty acid metal	oolism		
	Acute inflammatory response			Eatty acid motobolism	1		
	Leukocyte migration involved in inflammatory response			Steroid hormone biosynth	esis		
	Regulation of cytokine production in immune response			PPAR signaling pathway	6313		
	Complement			Glyoxylate and dicarboxyl	ate metabolism		
	B cell receptor signaling pathway			Starch and sucrose metal	oolism		
	Positive regulation of nfkb transcription factor activity			Bile acid biosynthesis			
	II2 stat5 signaling			Selenoamino acid Metabo	lism		
	Leukocyte transendothelial migration			Dimethyl branched chain	fatty acid β-oxidation		
	Acute inflammatory response to antigenic stimulus			Lysine degradation			
	T cell receptor signaling pathway			Glycolysis and gluconeog	enesis		
	Nfkb1 pathway			Porphyrin and chlorophyll	metabolism		
	Positive regulation of interferon gamma production			Purino pueloctidos povo l	higgynthogia		
	Response to type I interferon			D-imvo Linositol 1-4-5-tris	nhosnhate metabolism		
	Interleukin 6 secretion			D-imyo I-inositol 1-4-5-tris	phosphate degradation		
	Regulation of acute inflammatory response			Mono-unsaturated fatty a	cid β-oxidation		
	Positive regulation of the biosynthetic process			Vitamin E metabolism			
	lκ-b kinase nfkb signaling			Pantothenate and coa bio	synthesis		
	Chronic inflammatory response			Fatty acid elongation			
	Positive regulation of inflammatory response			Valine degradation			
	Response to interferon beta			2-oxocarboxylic acid meta	ibolism		
	Tnf biosynthetic process			3-phosphoinositide degra	dation		
	Interleukin 2 production			Lysine metabolism			
	Positive regulation of interleukin 2 biosynthetic process			Omega-3 fatty acid metal	oolism		
	Response to thf			Isoleucine degradation	esis		
	Inflammatory response to wounding			Proximal tubule bicarbona	te reclamation		
	Production of molecular mediator in inflammatory response			One carbon pool by folate			
	Regulation of acute inflammatory response			Insulin signal pathwav			
	Inflammatory cell apoptotic process			Seleno compound metabo	olism		
	Tumor necrosis factor mediated signaling pathway			Glycosyl phosphatidylinos	itol		
	P53 pathway			β-alanine metabolism			
	Nfkb signaling			Ribosome biogenesis in e	ukaryotes		
	Interleukin 2 biosynthetic process			RNA degradation			
	Cytokine production involved in inflammatory response			Alanine aspartate and glu	tamate metabolism		
	Positive regulation of cytokine production			Chrosphingelinid bigsunt	hesis ganglicaarias		
	Wound healing involved in inflammatory response			Givenspringulpid biosynt	ncais gangiioseries		
	Response to il-2			Glycosphingolinid hiosynt	hesis alobo series		
	Response to il-6			Other glycan Degradation			
	Type i interferon production			Insulin secretion			
	Macrophage inflammatory protein 1 alpha production			Prostaglandin formation fr	om arachidonate		
	Regulation of response to interferon gamma			Salivary secretion			
	Cellular response to interferon beta			Rara pathway			
	Positive regulation of tumor necrosis factor secretion			Chondroitin sulfate biosyr	thesis late stages		
				Circadian entrainment	-		
	LUMOL DECLOSIS JACIOL SECTEDOD			Anti inflammatory metabo	lites formation		
	Taf-R signaling nothway:			/ the initial initiatory initial bo			
	Tgf-β signaling pathway			Phospholipases			

Supplementary Figure 2. GSEA analysis of transcriptional signatures in the kidney and liver during aging.

(a, b) Heatmap showing GSEA analysis based on transcriptional changes with aging in kidney and liver for metabolism related terms (a) and inflammation related terms (b). The color represents enrichment significance in aged mice. Blue color represents down-regulated terms with aging, and red color represents up-regulated terms with aging.



Supplementary Figure 3. RT-qPCR analysis of typical inflammation-related genes and metabolism-related genes in the kidney and liver.

(a, b) RT-qPCR showing the relative expression of inflammation-related genes in the kidney (a) and liver (b) of young and old mice, (n = 3).

(c, d) RT-qPCR showing the relative expression of metabolism-related genes in the kidney (c) and liver (d) of young and old mice, (n = 3).

Data are presented as means \pm S.E.M. Data were analyzed by unpaired two-tailed *t*-test (a–d). * *P* < 0.05, ** *P* < 0.01.



Supplementary Figure 4. Epigenetic signatures of aged kidney and liver revealed by ATAC-seq.

(a) PCA of chromatin accessibility detected with ATAC-seq in the kidney (dark red) and liver (blue).(b, c) Ranking bar plot and scatter plot showing the correlation between promoter accessibility and gene expression in the kidney (b) and liver (c). Red bar represents upregulated peaks and genes in aged tissues, and blue bar represents downregulated peaks and genes in aged tissues.

(d) Circular plot showing distribution and accessibility of aging-associated peaks in the kidney (red), and liver (blue) on genome.

(e–j) Pie charts showing the proportions of distribution on genome for aging associated peaks. All peaks (e), open peaks (f) and closed peaks (g) in the kidney, and all peaks (h), open peaks (i) and closed peaks (j) in the liver are analyzed individually.



Supplementary Figure 5. Genome browser visualization of typical genes in the kidney and liver.

(a, b) Browser showing changes in the promoter accessibility and expression level of inflammationrelated genes in the kidney (a) and liver (b);

(c, d) Browser showing changes in the promoter accessibility and expression level of metabolism-related genes in the kidney (c) and liver (d).

Data were analyzed by unpaired two-tailed *t*-test (a–d). * P < 0.05, ** P < 0.01, *** P < 0.001.



Supplementary Figure 6. RT-qPCR analysis of selected genes showed in Genome Browser

(a, b) RT-qPCR showing the relative expression of selected inflammation (a) and metabolism (b) related genes showed in Genome Browser in the kidney (left) and liver (right) of young and old mice, (n = 3).

Data are presented as means \pm S.E.M. Data were analyzed by unpaired two-tailed *t*-test (a, b). * *P* < 0.05, ** *P* < 0.01, *** *P* < 0.001.

8	a Comi	monly Enriched moti	fs in aging-a	ssociated open	peaks	b	Comn	nonly Enriched motif	fs in aging-as	ssociated closed	peaks
[Motif	Name	Family	Enrichment score (kidney)	Enrichment score (liver)		Motif	Name	Family	Enrichment score (kidney)	Enrichment score (liver)
	ETGASTCATS	AP-1	bZIP	146	46.46		GITAATGATTAA	HNF1B	Homeobox	92.3	199.6
	Setgastcaess	ATF3	bZIP	157	44.02		SOTTAN	HNF1	Homeobox	81.61	172.3
	ASSAGGAAGI	EHF	ETS	224	144.5		SORAGHECAAACTECA	HNE4A	NR	65.88	187.2
	<u>¢¢¢¢</u> GGAAGI	ELF1	ETS	177	65.34		STACOLCANACOLCA		NR	22.00	107.2
	ASSAGGAAGI	ELF3	EIS	212	121.1		SUCCESSION CONTRACTOR	PPARA		33.99	176.5
	ASSACCAACT	ELF4 ELE5	EIS	300	100.0		45GG9GA8AGG4GA	RXR		23.91	121.3
	PASTTCCCGZ	ELFJ ELK1	ETS	243	10.21		CAAAGGICAS	ERRA	NR	22.93	66.16
	RASTICCOSE	FLK4	FTS	147	55.48		TGACCTITOSCOCA	PPARE	NR	18.89	112.2
	ACAGGAASTS	ERG	ETS	228	225.7		ITGASCIIIS	RARA	NR	18.63	64.18
	ACCCGGAAGT	ETS	ETS	149	59.19		STATE COLOR	EAR2	NR	17.19	72.49
	ACAGGAAGTG	ETS1	ETS	307	208.6		TGACCTTTQSSI	NUR77	NR	15.97	62 47
	ACCOGAAGE	ETV1	ETS	246	202.4		STREEASTERNAS	NE1	CTE	12.94	21.09
	SEALINCESS	ETV2	ETS	275	208.5		SCLODETSALADODS		ND	12.04	21.00
	CCCGGAAGES	ETV4	ETS	209	135.9		XEGILASAGGILA	1 K4		12.51	48.95
	TOTOLOGY	FLI1	EIS	256	188		REGACCIES	ESRRB		9.992	35.32
	SECTOR A ACT	CARDA	DZIP	240	41.5			FOXO3	Forkhead	8.637	85.1
	GANSICAANSI	IRE8	IRE	198	45.47		AXATATAAACA ®	FOXF1	Forkhead	8.552	58.96
	SATGASTCAL	JUNB	bZIP	168	42.57		SETGTTTACET	FOXK2	Forkhead	7.469	59.94
	AGAGGAAGTG	SPI1	ETS	282	145.3		STAATSA	NKX6.1	Homeobox	6.501	17.86
	AAASAGGAASTG	SPIB	ETS	278	57.48		SACAAPALISTOTIC	GRE	NR	6 221	11.64
	STGASTCATS	FOSL2	bZIP	187	34.05		TREAST	FOYDA	Forkhead	5.221	02.04
	SEATGASTCAIS	FRA2	bZIP	170	34.49		SSTUTTACXA			5.299	03.04
	SOTGAO TCAS	BATF	bZIP	156	39.03		LSAGGICA	IHKB		5.239	37.89
c Commonly Enriched motifs in aging-associated up-regulated genes d Commonly Enriched motifs in aging-associated down-regulated ge									ated genes		
	Motif	Name	Family	Enrichment score (kidney)	Enrichment score (liver)		Motif	Name	Family	Enrichment score (kidney)	Enrichment score (liver)
	ASAGGAAGTS AAAGAGGAACTS GAAGIGGAACT GAAGIGGAACT GGAACTGAAACT GGAACTGAAACT GGAACTGAAACT GGAACTGAACT	SP11 SPIB IRF8 ETS1-DISTAL SP11:IRF8 EWS:ERG RUNX-AML NFAT:AP1 RUNX NFKB-P65 BZIP:IRF JUN-AP1 NFKB-P65-REL	ETS ETS IRF ETS ETS Runt RHD RUNT BZIP BZIP RHD	31.74 30.14 24.87 23.46 22.5 20.06 11.99 11.86 11.05 8.797 7.111 6.088 5.889	14.15 12.29 3.474 7.563 3.591 5.668 5.307 3.667 3.362 3.331 4.485 5.501 5.435		SRADITICAAGUTICA	HNF4A	NR	9.338	12.49
	<u>STGASTCASS</u>	AP-1	bZIP	5.289	6.575						

Supplementary Figure 7. Commonly enriched TFs in the kidney and liver during aging based on ATAC-seq and RNA-seq.

(a, b) Commonly enriched motifs in aging-associated peaks in the kidney and liver. Commonly significantly enriched motifs in open peaks (a) and closed peaks (b) are shown.

(c, d) Commonly enriched motifs in aging-associated genes in the kidney and liver. Commonly significantly enriched motifs in up-regulated genes (a) and down-regulated genes (b) are shown. Motif analysis is performed using HOMER.



Supplementary Figure 8. Activities and expression changes of regulatory TFs in the kidney and liver during aging.

(a) Heatmap showing the activity changes of identified potential regulatory TFs in the kidney and liver during aging. The color represents activity changes during aging. Red represents increased activities and blue represents decreased activities during aging.

(b) Heatmap showing the expression changes of selected TFs in the kidney and liver during aging. The color represents gene expression changes during aging. Red represents increased gene expression and blue represents decreased gene expression during aging.



Supplementary Figure 9. RT-qPCR analysis of AP-1 and ETS family TFs in the kidney and liver

(a, b) RT-qPCR showing the relative gene expression of AP-1 and ETS family TFs in the kidney (a) and liver (b) of young and old mice, (n = 3).

Data are presented as means \pm S.E.M. Data were analyzed by unpaired two-tailed *t*-test (a, b). * *P* < 0.05, ** *P* < 0.01.



Response Figure 10. Validation of SPI1 in the kidney and liver by FACS

(a) RT-qPCR showing the relative gene expression of *SP11* in sorted $F4/80^+$ cell as compared to $F4/80^-$ cells in the kidney (left) and liver (right) of aged mice. O1, O2, and O3 represents different mice.

(b) Quantification of the proportion of $F4/80^+$ cells in the kidney and liver of young and old mice, (n=3).

Data are presented as means \pm S.E.M. Data were analyzed by unpaired two-tailed *t*-test (a, b). * *P* < 0.05, ** *P* < 0.01.



b

Kidney SPI1



Top: SA-β-gal Bottom: 📃 D

Bottom: DAPI SPI1

Supplementary Figure 11. The detection of cellular senescence in aged kidney.

(a) Activation of c-JUN in senescence cells was examined by co-staining for SA- β -Gal activity (top) and c-JUN by immunofluorescence (bottom) in aged kidney. SA- β -gal⁺ cells were predominantly observed in the tubular epithelium, distributing throughout both the renal cortex and medulla. c-JUN was observed to be expressed in the nuclei of renal tubal epithelial cells, in both the cortex and the medullar. And some of the c-Jun⁺ cells co-expressed SA- β -gal activity.

(b) Activation of SPI1 in senescence cells was examined by co-staining for SA- β -Gal activity (top) and SPI1 by immunofluorescence (bottom) in aged kidney. SPI1 was localized in irregular nuclei located in the space between renal tubules or around the glomerulus. And some of the SPI1⁺ cells exhibited weak SA- β -gal activity.

The regions of the renal cortex and the medullar were randomly photographed. And c-JUN⁺ or SPI1⁺ nuclei are labeled with white arrows and active SA- β -gal nuclei are labeled with yellow arrows. Scale bar = 50 μ m.



Liver SPI1



Top: SA-β-gal Bottom: DAPI **E** SPI1

Supplementary Figure 12. The detection of cellular senescence in aged liver.

(a, b) Activation of c-JUN (a) or SPI1 (b) in senescence cells was examined by co-staining for SA- β -Gal activity (top) and TFs by immunofluorescence (bottom) in aged liver. c-JUN⁺ nuclei was rarely co-localized with active SA- β -gal, while some of the SPI1⁺ nuclei showed co-localization with SA- β -gal in the interstitial space of the hepatic cells.

The regions of liver were randomly photographed. c-JUN⁺ or SPI1⁺ nuclei are labeled with white arrows and active SA- β -gal nuclei are labeled with yellow arrows. Scale bar = 50 μ m.