S1

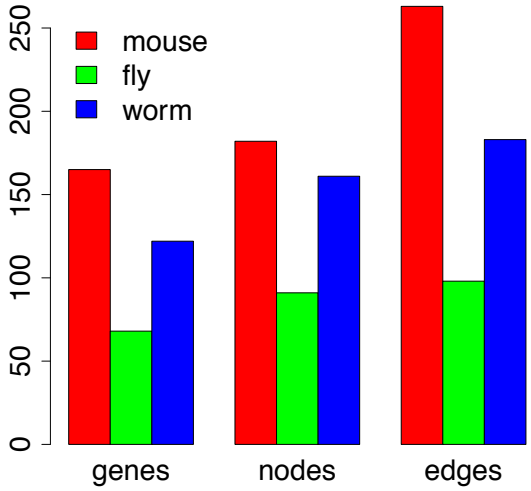
Mus musculus

Pappa
Proteolysis
Proteolysis
Lep_Leptin
Igfbp1
Igfbp2
Igfbp3
Igfbp4
Igfbp5
Igfbp6
Igfbp7
klotho_pept
pH>7.9
Ins1
Ins2
Igf1
Igf2
Targets for lysosomal degradation
Plasma membrane
Insr
Igf1r
Igf2r
Kl_klotho
Insrr
Itga1-10
Itgb1
Lepr
Cell
Flot2
Flot1
c_Cbl
Sorbs1_CAP
Cbl
Sh2b2_APS
c_Crk
Crk
Rapgef1_GRF2
Rhoq_TC10
Slc2a4_Glut4
Glucose uptake
Sh2b1
Grb14
Irs3
Irs4
Asb4
Irs1
Irs2
Ptprf_LAR
Jak2
Shc1
Gnb2l1_RACK1
Fyn
Jak1
Inpp5d_SHIP1
Inppl1_SHIP2
Ptpn11_Shp2
Fer
c_PI3K
Pik3r1_P85
Pik3ca_P110
Pten
Sh2b3_Lnk
Grb2
Gab1
c_Grb10_Nedd4
Nedd4
Grb10
Rps6_S6
Protein synthesis
Autophagy
TOR
Rps6kb1_p70S6K
c_atg
Atg13
Ulk1
Rb1cc1
c_mTORC1
Rptor
Mlst8_GbetaL
Mtor
Eif4ebp1_4E-BP1
Akt1s1_PRAS40
c_AMPK
Prkaa1_AMPKa1
Prkab1_AMPKb
Prkag3_Ampkg3
c_CSNK2
Csnk2a1
Csnk2a2
Csnk2b
c_eIF4F
Eif4e
Eif4g1
Eif4a1
Deptor
Btrc_βTrCP
Eef2
Eef2k
Pdcd4
Rheb
Eif4b
Prkca_Pkcalpha
Prkci_aPKCiota
Prkcz_aPKCzeta
Prkcg_ Pkcgamma
Pdpk1_Pdk1
Prkcb_Pkcbeta
Gys2
Gys1
Rps6ka1_Rsk1
Gsk3a
Gsk3b
Tbc1d4_AS160
Akt2
Akt3
Akt1
c_mTORC2
Rictor
Prr5_Protor1
Mtor
Mlst8_Gbetal
Mapkap1_Sin1
Pml
Rasgrf1
Sos2
Sos1
MAPK/ERK
Eras
Nras
Kras
Hras1
Rras
Rras2
Mras
Ralgds
Rala
Raf1
Ksr1
Map2k2_Mek2
Map2k1_Mek1
Mapk3_Erk1
Mapk1_Erk2
Mknk2
Mknk1
Src
Arrb2_Beta-arrestin-2
JNK
Map3k1_MEKK1
Map2k4
Map2k7
Mapk9_JNK2
Mapk8_JNK1
Mapk10_JNK3
Sgk1
Sgk2
Sgk3
Crebbp
Ywhae_14-3-3E
Bad
Wnt signalling
Ctnnb1
c_TSC
Tsc2
Tsc1
Stk11_LKB1
Stk4_MST1
Sirt1
Oxidative Stress
Nucleus
Jun
Fos
Foxo1
Foxo4
Foxo3
Foxo6
Myc
Rps6ka3_Rsk2
Atf4
Hif1a
Ep300
Cops5_Jab1
E2f1
Elk1
Trp53
Proliferation_diferentiation
longevity
mouse, fly & worm
mouse, worm; not fly
mouse, fly; not worm
mouse only

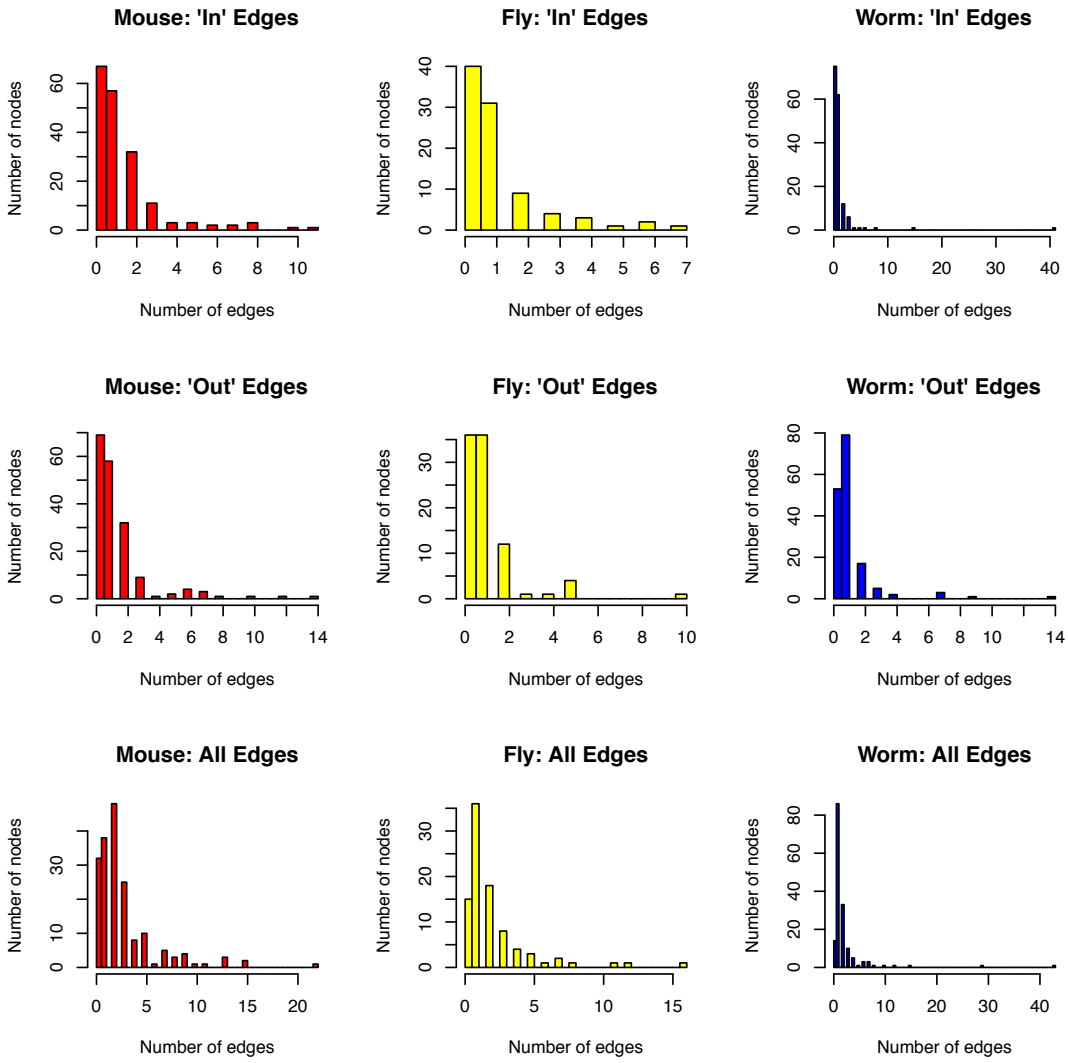
S2.

Mouse	Fly	Worm	Note	Pathway
NA	ImpL2	zig-2,zig-3,zig-4	worm genes not in pathway	IIS
Ins1, Ins2, Igf1, Igf2	Ilp1, … Ilp7	ins-1, … ins-40	non-orthologues	IIS
Insr, Insrr, Igf1r	InR	daf-2		IIS
Irs1, Irs2. Irs3, Irs4	chico	ist-1	worm insulin receptor substrate homologue from OrthoDB	IIS
Sh2b1, Sh2b2, Sh2b3	Lnk	NA		IIS
Pik3cd, Pik3cb, Pik3ca, Pik3cg	Pi3K68D, Pi3K92E	age-1	age-1 is orthologue to the fly gene and the human PIK3CA (TreeFam). The fly gene is absent from the model	IIS
Pik3r1, Pik3r2, Pik3r3	Pi3K21B	aap-1		IIS
Pdpk1	Pk61C	pdk-1		IIS
Akt1, …, Akt3	Akt1	akt-1, akt-2		IIS
Sgk1, …, Sgk3	NA	sgk-1		IIS
Foxo1, Foxo3, Foxo4, Foxo6	foxo	daf-16		IIS
Ywhae	14-3-3epsilon	ftt-2, par-5		IIS
Veph1	melt	K10B4.3	gene not in the worm/mouse pathway	IIS
Stk3, Stk4	hpo	cst-1, cst-2		IIS
Phlpp1, Phlpp2	Phlpp	F43C1.1	gene not in the worm/mouse pathway	IIS
NA	wdp	NA		IIS
Pten	Pten	daf-18		IIS
NA	B4	NA		IIS
Cyth1, …, Cyth4	step	grp-1	gene not in the worm/mouse pathway	IIS
Grb2	drk	sem-5	fly gene not in pathway	IIS
Gnb2l1	Rack1	rack-1	only in mouse pathway	IIS
mTor	Tor	let-363	worm Tor orthologue identified through Treefam (not compara)	TOR
Ulk1	Atg1	unc-51		TOR
Eif4b	eIF-4B	drr-2, H05C05.1	phylome orthology	TOR
Nup62	Nup62	unc-14	fly and mouse genes not in pathway models	TOR
Rps6	RpS6	rps-6		TOR
Rheb	Rheb	rheb-1		TOR
Akt1s1	L	NA	orthologue present only in phylome orthology	TOR
Ddit4, Ddit4l	scyl	NA	only in the fly pathway	TOR
Ddit4, Ddit4l	chrb	NA	only in the fly pathway	TOR
Prkaa1	SNF1A	aak-2		TOR
Stk11	lkb1	par-4		TOR
Tsc2	gig	NA		TOR
Tsc1	Tsc1	NA		TOR
Casp9	Dredd	ced-3	only in fly pathway	TOR
Rraga, Rragb	RagA	raga-1	not in mouse pathway	TOR
Rragc, Rragd	RagC	ragc-1	only in fly pathway	TOR
Rptor	raptor	daf-15		TOR
Mlst8	Lst8	C10H11.8		TOR
Mapkap1	Sin1	sinh-1		TOR
Rictor	rictor	rict-1		TOR
Rps6kb1, Rps6kb2	S6k	rsks-1		TOR
Eif4g3, Eif4g1	eIF4G	ifg-1		TOR
Eef2k	NA	efk-1	absent in fly, not in worm pathway	TOR
Crtc1	TORC	crtc-1	only in fly pathway	TOR
Eif4ebp1, Eif4ebp2, Eif4ebp3	Thor	NA		TOR
Sik1, Sik2	CG4290	kin-29	only in fly pathway	TOR
Eif4e	eIF-4E, eIF4E-3, …, eIF4E-7	ife-1, ife-2, ife-3, ife-5		TOR

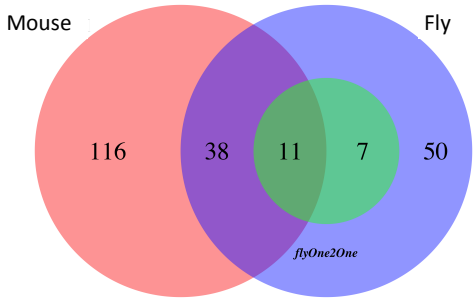
S3

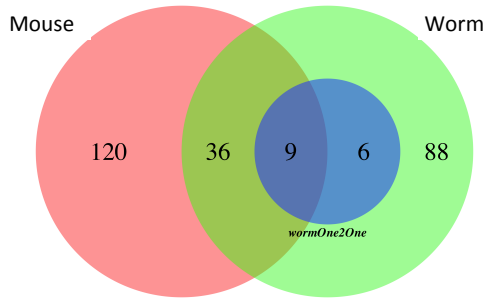


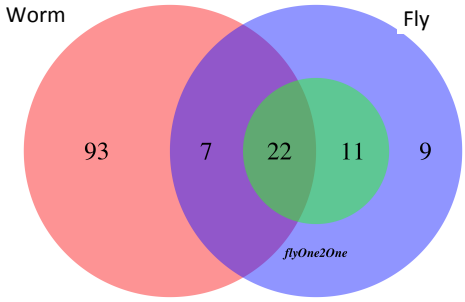
S3.A Histogram comparing the numbers of genes, nodes and edges present in the curated models of the IIS/TOR pathways in each of the three organisms.



S3.B Comparing the distribution of number of edges per node in each organism. The comparison is done for “in-bound” edges, “out-bound” edges and “all” edges.







S3.C Venn diagrams comparing the orthologues of the different species within the pathway models. For each diagram the circle on the left-hand-side shows the number of genes present in the pathway of a particular organism. The circle on the right hand-side shows all orthologous genes that are present in the pathway of the other organism. Inner circles distinguish the one-to-one orthologues between each pair of organisms.

organism	**cross-talk type**	**interactions**	**multiple gene copies**
mouse	MAPK/ERK to IIS	Mapk3 -| Gab1 -> Pi3k	NO
fly	MAPK/ERK to IIS	orthologues exist, but no interactions found	NO
worm	MAPK/ERK to IIS	no orthologue for Gab1	NO
mouse	IIS to MAPK/ERK	Grb2 -> Sos1	NO
fly	IIS to MAPK/ERK	orthologues exist, but no interactions found	NO
worm	IIS to MAPK/ERK	orthologues exist, but no interactions found	NO
mouse	IIS to MAPK/ERK	src -> Raf1	NO
fly	IIS to MAPK/ERK	no orthologue for src	NA
worm	IIS to MAPK/ERK	no orthologue for src	NA

mouse	MAPK/ERK to TOR	Mapk1 -> Rps6ka1	NO
fly	MAPK/ERK to TOR	orthologues exist, but no interactions found	NO
worm	MAPK/ERK to TOR	mpk-1 - rskn-1 (physical, undirectional from Y2H screen, Li et al Science 2004)	NO
mouse	IIS to JNK	Gsk3b -> Map3k1/Map3k4	NO
fly	IIS to JNK	orthologues exist, but no interactions found	NO
worm	IIS to JNK	orthologues exist, but no interactions found	NO
mouse	JNK to IIS	Mapk8 -| Irs1/Irs2	YES
fly	JNK to IIS	bsk -| chico	NO
worm	JNK to IIS	jnk-1 -| ist-1	NO
mouse	IIS to TOR	Akt1 -| Akt1s1	YES
fly	IIS to TOR	Akt1 -| L	NO
worm	IIS to TOR	no orthologue for Akt1s1	NA
mouse	IIS to TOR	Akt1 -| Tsc2	YES
fly	IIS to TOR	Akt1 -| gig	NO
worm	IIS to TOR	no orthologue for Tsc2	NA
mouse	IIS to TOR	Gsk3b -| Tsc2	NO
fly	IIS to TOR	sgg -| gig	NO
worm	IIS to TOR	no orthologue for Tsc2	NA
mouse	TOR to IIS	AMPK -> Insr	NO
fly	TOR to IIS	orthologues exist, but no interactions found	NO
worm	TOR to IIS	orthologues exist, but no interactions found	NO
mouse	TOR to IIS	Rps6kb1 -| Irs1	YES
fly	TOR to IIS	S6k -| chico	NO
worm	TOR to IIS	orthologues exist, but no interactions found	NO
mouse	TOR to IIS	TORC2 -> Akt1	YES
fly	TOR to IIS	TORC2 -> Akt1	NO
worm	TOR to IIS	TORC2 -> akt-1	YES

S3.D Table summarising cross-talk points between pathways within the mouse model, the existence of similar interactions between orthologues in flies and worms and whether a cross-talk point involves a gene with multiple copies.

S4. Results on Ins1 and Irs1 in all three organisms

MOUSE Reducing Longevity (Ins1)-similar for Ins2

Ins1 ↓	Igf1r ↓	Gnb2l1_RA	Src ↑	Akt1 ↑	Foxo4 ↓	longevity ↓
Ins1 ↓	Igf1r ↓	Gnb2l1_RA	Src ↑	Akt1 ↑	Foxo3 ↓	longevity ↓
Ins1 ↓	Igf1r ↓	Gnb2l1_RA	Src ↑	Akt1 ↑	Foxo1 ↓	longevity ↓

MOUSE Extending Longevity (Ins1)-similar for Ins2

Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk3 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo4 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo4 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo4 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo4 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk2 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk2 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk3 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk2 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo3 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo3 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo3 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk1 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk3 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk3 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk2 ↓	Foxo1 ↑ longevity ↑
Ins1 ↓	Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo3 ↑ longevity ↑

MOUSE Reducing Longevity (Irs1)-similar for Irs2

Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓

MOUSE Extending Longevity (Irs1)-similar for Irs2

Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo3 ↑	longevity ↑
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk1 ↓	Foxo1 ↑	longevity ↑
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk3 ↓	Foxo1 ↑	longevity ↑
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo4 ↑	longevity ↑
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Sgk2 ↓	Foxo1 ↑	longevity ↑
Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk	Akt1 ↓	Foxo1 ↑	longevity ↑

FLY Reducing Longevity (Ilp1)-similar for Ilp2-7

Ilp1 ↓	InR ↓	Lnk_dSH2B	c_Pi3K ↓	Pk61C_dPDK	S6k ↓	chico_IRS ↑	c_Pi3K ↑	Akt1_PKB ↑ foxo ↓ longevity ↓
Ilp1 ↓	InR ↓	chico_IRS ↓	c_Pi3K ↓	Pk61C_dPDK	S6k ↓	chico_IRS ↑	c_Pi3K ↑	Akt1_PKB ↑ foxo ↓ longevity ↓

FLY Extending Longevity (Ilp1)-similar for Ilp2-7

Ilp1 ↓	InR ↓	Lnk_dSH2B	c_Pi3K ↓	Akt1_PKB ↓	foxo ↑	longevity ↑
Ilp1 ↓	InR ↓	chico_IRS ↓	c_Pi3K ↓	Akt1_PKB ↓	foxo ↑	longevity ↑

FLY Reducing Longevity (chico)

chico_IRS ↓	c_Pi3K ↓	Akt1_PKB ↓	L_PRAS40 ↑	c_Tor_C1 ↓	c_Tor_C2 ↑	Akt1_PKB ↑	foxo ↓ longevity ↓

FLY Extending Longevity (chico)

chico_IRS ↓	c_Pi3K ↓	Akt1_PKB ↓	foxo ↑	longevity ↑

WORM Reducing Longevity (ins-1)-similar for ins-2:ins-40

ins_1 ↓	daf_2 ↓	ist_1 ↓	let_60 ↓	skn_1 ↓	longevity ↓

WORM Extending Longevity (ins-1)-similar for ins-2:ins-40

ins_1 ↓	daf_2 ↓	ist_1 ↓	daf_16 ↑	longevity ↑

WORM Reducing Longevity (ist-1)

ist_1 ↓	let_60 ↓	skn_1 ↓	longevity ↓

WORM Extending Longevity (ist-1)

ist_1 ↓	daf_16 ↑	longevity ↑

MOUSE Reducing Longevity Igf1r

Igf1r ↓	Gnb2l1_RA Src ↑	Akt1 ↑	Foxo3 ↓	longevity ↓	
Igf1r ↓	Gnb2l1_RA Src ↑	Akt1 ↑	Foxo4 ↓	longevity ↓	
Igf1r ↓	Gnb2l1_RA Src ↑	Akt1 ↑	Foxo1 ↓	longevity ↓	

MOUSE Extending Longevity Igf1r

Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk3 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo4 ↑	longevity ↑
Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk1 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk3 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo3 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo4 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk1 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk2 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo1 ↑	longevity ↑
Igf1r ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo3 ↑	longevity ↑
Igf1r ↓	Irs2 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk2 ↓	Foxo1 ↑	longevity ↑

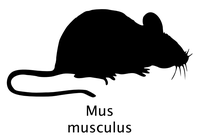
MOUSE Reducing Longevity Insr

Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo4 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Rps6kb1_p70S6K ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo3 ↓	longevity ↓
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Prkca_Pkcalpha ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Prkcb_Pkcbeta ↓	Gsk3b ↑	E2f1 ↓	Sirt1 ↓	Foxo1 ↓	longevity ↓

MOUSE Extending Longevity Insr

Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo3 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk1 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo4 ↑	longevity ↑
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk3 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk3 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk2 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs1 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk1 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo1 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo4 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Akt1 ↓	Foxo3 ↑	longevity ↑
Insr ↓	Irs4 ↓	c_PI3K ↓	Pdpk1_Pdk Sgk2 ↓	Foxo1 ↑	longevity ↑

S5.A. Differential expression in liver



Pappa
Proteolysis
Proteolysis
Igfbp1
Igfbp2
Igfbp3
Igfbp4
Igfbp5
Igfbp6
Igfbp7
Lep_Leptin
Ins1
Ins2
Igf1
Igf2
Targets for lysosomal degradation
klotho_peptide
pH>7.9
Plasma membrane
Insr
Igf1r
Igf2r
Kl_klotho
Insrr
Itga8
Itga4
Itga1
Itga9
Itga3
Itga11
Itga7
Itga10
Itga6
Itga5
Itga2
Itgb1
Lepr
Cell
Flot2
Flot1
c_Cbl
Sorbs1_CAP
Cbl
Sh2b2_APS
c_Crk
Crk
Rapgef1_GRF2
Rhoq_TC10
Slc2a4_Glut4
Glucose uptake
Sh2b1
Grb14
Ptprf_LAR
Irs3
Irs4
Asb4
Irs1
Irs2
Jak2
Shc1
Gnb2l1_RACK1
Fyn
Ptpn11_Shp2
Inpp5d_SHIP1
Inppl1_SHIP2
Jak1
Fer
c_PI3K
Pik3r1_P85
Pik3ca_P110
Pten
Sh2b3_Lnk
Grb2
Gab1
c_Grb10_Nedd4
Nedd4
Grb10
Rps6_S6
Protein synthesis
Autophagy
TOR
c_atg
Atg13
Ulk1
Rb1cc1
+pT
+pS855pS859
Rps6kb1_p70S6K
c_mTORC1
Rptor
Mlst8_GbetaL
Mtor
Eif4ebp1_4E-BP1
Akt1s1_PRAS40
c_AMPK
Prkaa1_AMPKa1
Prkab1_AMPKb
Prkag3_Ampkg3
Deptor
Btrc_βTrCP
+Ubq
c_eIF4F
Eif4e
Eif4g1
Eif4a1
Eef2
Eef2k
Pdcd4
Rheb
Eif4b
Rps6ka1_Rsk1
Prkci_aPKCiota
Prkcz_aPKCzeta
Prkcg_ Pkcgamma
Pdpk1_Pdk1
Prkca_Pkcalpha
Prkcb_Pkcbeta
c_CSNK2
Csnk2a1
Csnk2a2
Csnk2b
Gys2
Gys1
Gsk3a
Gsk3b
Tbc1d4_AS160
Akt2
Akt3
Akt1
Src
Arrb2_Beta-arrestin-2
c_mTORC2
Rictor
Prr5_Protor1
Mtor
Mlst8_GbetaL
Mapkap1_Sin1
Pml
c_TSC
Tsc2
Tsc1
Dissasembles the active complex
Wnt signalling
Ctnnb1
Prevents degradation
Bad
Ywhae_14-3-3E
Crebbp
Sgk1
Sgk2
Sgk3
Stk4_MST1
Stk11_LKB1
Sirt1
Oxidative Stress
MAPK/ERK
Eras
Nras
Kras
Hras1
Ras
Rras2
Mras
Ralgds
Rala
Ksr1
Raf1
Map2k2_Mek2
Map2k1_Mek1
Mapk3_Erk1
Mapk1_Erk2
Mknk2
Mknk1
JNK
Map3k1_MEKK1
Map2k4
Map2k7
Mapk9_JNK2
Mapk10_JNK3
Mapk8_JNK1
+ps Targets for Degradation
Nucleus
Jun
Fos
Foxo1
Foxo4
Foxo6
Foxo3
-promotes ubiquitination through physical interaction
E2f1
Myc
Atf4
Hif1a
Ep300
Copss_Jab1
-Ac
Trp53
Rps6ka3_Rsk2
Proliferation.diferentiation
Elk1
longevity

Liver Results

Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓

Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓

Foxo1 ↓ longevity ↓

Foxo3 ↓ longevity ↓

Prkcb_Pkcb Gsk3b ↓ Map2k4 ↓ Mapk8_JNK Sirt1 ↓ Foxo4 ↓ longevity ↓
Prkcb_Pkcb Gsk3b ↓ Map2k4 ↓ Mapk8_JNK Sirt1 ↓ Foxo1 ↓ longevity ↓
Prkcb_Pkcb Gsk3b ↓ Map2k4 ↓ Mapk8_JNK Sirt1 ↓ Foxo3 ↓ longevity ↓

Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo3 ↓ longevity ↓
Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo4 ↓ longevity ↓
Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo1 ↓ longevity ↓

Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Sgk3 ↑ Foxo1 ↓ longevity ↓
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Sgk1 ↑ Foxo1 ↓ longevity ↓
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Akt1 ↑ Foxo1 ↓ longevity ↓
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Akt1 ↑ Foxo4 ↓ longevity ↓
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Sgk2 ↑ Foxo1 ↓ longevity ↓
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Akt1 ↑ Foxo3 ↓ longevity ↓

Igfbp3 ↑ Igf1 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo1 ↓ longevity ↓
Igfbp3 ↑ Igf2 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo4 ↓ longevity ↓
Igfbp3 ↑ Igf1 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo3 ↓ longevity ↓
Igfbp3 ↑ Igf2 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo1 ↓ longevity ↓
Igfbp3 ↑ Igf1 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo4 ↓ longevity ↓
Igfbp3 ↑ Igf2 ↓ Igf1r ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo3 ↓ longevity ↓

Itga8 ↓ Itgb1 ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo3 ↓ longevity ↓
Itga8 ↓ Itgb1 ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo1 ↓ longevity ↓
Itga8 ↓ Itgb1 ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Foxo4 ↓ longevity ↓

Itga9 ↑ Itgb1 ↑ Gnb2l1_RA Src ↓ Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Itga9 ↑ Itgb1 ↑ Gnb2l1_RA Src ↓ Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Itga9 ↑ Itgb1 ↑ Gnb2l1_RA Src ↓ Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓

Igf1r ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igf1r ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑

Prkcb_Pkcb Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑

Jak1 ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Jak1 ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑

Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Akt1 ↑ Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Prkcb_Pkcb Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Prkca_Pkca Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑
Asb4 ↓ Irs4 ↑ c_PI3K ↑ Pdpk1_Pdk Rps6kb1_p Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑

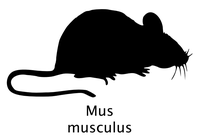
Igfbp3 ↑ Igf2 ↓ Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igfbp3 ↑ Igf2 ↓ Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igfbp3 ↑ Igf1 ↓ Igf1r ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igfbp3 ↑ Igf1 ↓ Igf1r ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igfbp3 ↑ Igf2 ↓ Igf1r ↓ Irs2 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Igfbp3 ↑ Igf2 ↓ Igf1r ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑

Insr ↓ Irs4 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑
Insr ↓ Irs1 ↓ c_PI3K ↓ Pdpk1_Pdk Akt1 ↓ Foxo4 ↑ longevity ↑

Foxo1 ↓ Sirt1 ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑

Itga8 ↓ Itgb1 ↓ Gnb2l1_RA Src ↑ Akt1 ↑ Gsk3b ↓ E2f1 ↑ Sirt1 ↑ Foxo4 ↑ longevity ↑

Itga9 ↑ Itgb1 ↑ Gnb2l1_RA Src ↓ Akt1 ↓ Foxo4 ↑ longevity ↑



S5.B. Differential expression in lung

Pappa
Proteolysis
Proteolysis
Igfbp1
Igfbp2
Igfbp3
Igfbp4
Igfbp5
Igfbp6
Igfbp7
Lep_Leptin
Ins1
Ins2
Igf1
Igf2
Targets for lysosomal degradation
klotho_peptide
pH>7.9
Plasma membrane
Insr
Igf1r
Igf2r
Kl_klotho
Insrr
Lepr
Itga9
Itga7
Itga8
Itga3
Itga11
Itga10
Itga6
Itga4
Itga1
Itgb1
Itga5
Itga2
Cell
Flot2
Flot1
c_Cbl
Sorbs1_CAP
Cbl
Sh2b2_APS
c_Crk
Crk
Rapgef1_GRF2
Rhoq_TC10
Slc2a4_Glut4
Glucose uptake
Sh2b1
Grb14
Ptprf_LAR
Irs3
Irs4
Asb4
Irs1
Irs2
Jak2
Shc1
Gnb2l1_RACK1
Fyn
Ptpn11_Shp2
Inpp5d_SHIP1
Inppl1_SHIP2
Fer
Jak1
c_PI3K
Pik3r1_P85
Pik3ca_P110
PIP3
Pten
Sh2b3_Lnk
Grb2
Gab1
c_Grb10_Nedd4
Nedd4
Grb10
Rps6_S6
Protein synthesis
Autophagy
TOR
c_atg
Atg13
Ulk1
Rb1cc1
+pT
+pS855pS859
Rps6kb1_p70S6K
c_mTORC1
Rptor
Mlst8_GbetaL
Mtor
Akt1s1_PRAS40
Eif4ebp1_4E-BP1
c_AMPK
Prkaa1_AMPKa1
Prkab1_AMPKb
Prkag3_Ampkg3
c_eIF4F
Eif4e
Eif4g1
Eif4a1
Deptor
Btrc_βTrCP
Ubq
Eef2
Eef2k
Pdcd4
Rheb
Eif4b
Rps6ka1_Rsk1
Prkci_aPKCiota
Prkcz_aPKCzeta
Prkcg_ Pkcgamma
Pdpk1_Pdk1
Prkca_Pkcalpha
Prkcb_Pkcbeta
c_CSNK2
Csnk2a1
Csnk2a2
Csnk2b
Gys2
Gys1
Gsk3a
Gsk3b
Tbc1d4_AS160
Akt2
Akt3
Akt1
Src
Arrb2_Beta-arrestin-2
c_mTORC2
Rictor
Prr5_Protor1
Mtor
Mlst8_GbetaL
Mapkap1_Sin1
Pml
c_TSC
Tsc2
Tsc1
Dissasembles the active complex
Wnt signalling
Ctnnb1
Prevents degradation
Bad
Ywhae_14-3-3E
Crebbp
Sgk1
Sgk2
Sgk3
Stk4_MST1
Stk11_LKB1
Sirt1
Oxidative Stress
MAPK/ERK
Rasgrf1
Sos2
Sos1
Eras
Nras
Kras
Hras1
Ras
Rras2
Mras
Ralgds
Rala
Raf1
Ksr1
Map2k2_Mek2
Map2k1_Mek1
Mapk3_Erk1
Mapk1_Erk2
Mknk2
Mknk1
JNK
Map3k1_MEKK1
Map2k4
Map2k7
Mapk9_JNK2
Mapk10_JNK3
Mapk8_JNK1
+ps Targets for Degradation
Nucleus
Jun
Fos
Foxo1
Foxo6
Foxo4
Foxo3
Myc
Atf4
Hif1a
Ep300
Rps6ka3_Rsk2
Proliferation.diferentiation
Elk1
Cops5_Jab1
Trp53
-Ac
-promotes ubiquitination through physical interaction
E2f1
longevity

Lung Results

Foxo1 ↓ longevity ↓

Foxo3 ↓ longevity ↓

Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo4 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Akt1 ↑	Foxo3 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs1 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk1 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Insr ↑	Irs4 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk3 ↑	Foxo1 ↓	longevity ↓
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Irs2 ↑	c_PI3K ↑	Pdpk1_Pdk Sgk2 ↑	Foxo1 ↓	longevity ↓

Igfbp3 ↓	Igf2 ↑	Igf1r ↑	Gnb2l1_RA	Src ↓	Akt1 ↓	Foxo4 ↑	longevity ↑
Igfbp3 ↓	Igf1 ↑	Igf1r ↑	Gnb2l1_RA	Src ↓	Akt1 ↓	Foxo4 ↑	longevity ↑

Foxo1 ↓	Sirt1 ↓	E2f1 ↑	Sirt1 ↑	Foxo4 ↑	longevity ↑

Mus musculus

S5.C. Differential expression in thymus

Pappa
Proteolysis
Proteolysis
Igfbp1
Igfbp2
Igfbp3
Igfbp4
Igfbp5
Igfbp6
Igfbp7
Lep_Leptin
Klotho_peptide
pH>7.9
Ins1
Ins2
Igf1
Igf2
Targets for lysosomal degradation
Plasma membrane
Insr
Igf1r
Igf2r
Kl_klotho
Insrr
Itga8
Itga9
Itga7
Itga4
Itga3
Itga11
Itga10
Itga6
Itga1
Itgb1
Itga5
Itga2
Lepr
Cell
Flot2
Flot1
c_Cbl
Sorbs1_CAP
Cbl
Sh2b2_APS
c_Crk
Crk
Rapgef1_GRF2
Rhoq_TC10
Slc2a4_Glut4
Glucose uptake
Sh2b1
Grb14
Ptprf_LAR
Irs3
Irs4
Asb4
Irs1
Irs2
Jak2
Shc1
Gnb2l1_RACK1
Fyn
Ptpn11_Shp2
Inpp5d_SHIP1
Inppl1_SHIP2
Fer
Jak1
c_PI3K
Pik3r1_P85
Pik3ca_P110
Pten
Sh2b3_Lnk
Grb2
Gab1
+PIP3
c_Grb10_Nedd4
Nedd4
Grb10
Rps6_S6
Protein synthesis
Autophagy
TOR
c_atg
Atg13
Ulk1
Rb1cc1
+pS855pS859
Rps6kb1_p70S6K
c_mTORC1
Rptor
Mlst8_GbetaL
Mtor
Eif4ebp1_4E-BP1
Akt1s1_PRAS40
c_AMPK
Prkaa1_AMPKa1
Prkab1_AMPKb
Prkag3_Ampkg3
Deptor
Btrc_βTrCP
+Ubq
c_eIF4F
Eif4e
Eif4g1
Eif4a1
Eef2
Eef2k
Pdcd4
Rheb
Eif4b
Rps6ka1_Rsk1
Prkci_aPKCiota
Prkcz_aPKCzeta
Prkcg_ Pkcgamma
Pdpk1_Pdk1
Prkca_Pkcalpha
Prkcb_Pkcbeta
c_CSNK2
Csnk2a1
Csnk2a2
Csnk2b
Gys2
Gys1
Gsk3a
Gsk3b
Tbc1d4_AS160
Akt2
Akt3
Akt1
Src
Arrb2_Beta-arrestin-2
c_mTORC2
Rictor
Prr5_Protor1
Mtor
Mlst8_GbetaL
Mapkap1_Sin1
Pml
c_TSC
Tsc2
Tsc1
Dissasembles the active complex
Wnt signalling
Ctnnb1
Prevents degradation
Bad
Ywhae_14-3-3E
Crebbp
Sgk1
Sgk2
Sgk3
Stk4_MST1
Stk11_LKB1
Sirt1
Oxidative Stress
MAPK/ERK
Rasgrf1
Sos2
Sos1
Eras
Nras
Kras
Hras1
Ras
Rras2
Mras
Ralgds
Rala
Raf1
Ksr1
Map2k2_Mek2
Map2k1_Mek1
Mapk3_Erk1
Mapk1_Erk2
Mknk2
Mknk1
JNK
Map3k1_MEKK1
Map2k4
Map2k7
Mapk9_JNK2
Mapk10_JNK3
Mapk8_JNK1
+ps Targets for Degradation
Nucleus
Jun
Fos
Foxo1
Foxo4
Foxo6
Foxo3
Myc
Atf4
Hif1a
Ep300
E2f1
-promotes ubiquitination through physical interaction
Rps6ka3_Rsk2
Proliferation.diferentiation
Elk1
Cops5_Jab1
-Ac
Trp53
longevity

Thymus Results

Rictor ↓ c_mTORC2 Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Rictor ↓ c_mTORC2 Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Rictor ↓ c_mTORC2 Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓

Foxo1 ↓ longevity ↓

Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Pdpk1_Pdk Prkcb_Pkcb Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Pdpk1_Pdk Prkcb_Pkcb Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Pdpk1_Pdk Prkcb_Pkcb Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓
Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Pdpk1_Pdk Prkca_Pkca Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo1 ↓ longevity ↓
Pdpk1_Pdk Akt1 ↓ Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo4 ↓ longevity ↓
Pdpk1_Pdk Rps6kb1_p Gsk3b ↑ E2f1 ↓ Sirt1 ↓ Foxo3 ↓ longevity ↓

Foxo4 ↓ longevity ↓

Pdpk1_Pdk Akt1 ↓ Foxo3 ↑ longevity ↑

Rictor ↓ c_mTORC2 Akt1 ↓ Foxo3 ↑ longevity ↑

Foxo1 ↓ Sirt1 ↓ E2f1 ↑ Sirt1 ↑ Foxo3 ↑ longevity ↑