Supplementary Table S1. Summary of input signals and chromatin effector proteins for IIS signaling pathway controlling *Drosophila* lifespan. *Drosophila* and human protein symbols are provided according to the FlyBase annotation (March 29, 2022; http://flybase.org/). Alternative protein symbols (synonyms) are indicated within brackets.

Components	Human orthologs	Effect(s) on lifespan	Reference(s)
Ilp1 **Insulin-like peptide 1** (CG14173)	IGF1 IGF2	-	-
Ilp2 **Insulin-like peptide 2** (CG8167)	IGF1 IGF2	Knockout of *Ilp2* results in a median adult lifespan extension of 9% and 13% for males and females, respectively. Partial genetic ablation of the neurosecretory Ilp-producing cells that reside in the brain and are the primary producers of Ilp2, Ilp3 and Ilp5 in the adult body resulted in median lifespan increase by 10.5% in males and 18.5% and 33.5% in virgin and mated females, respectively.	[1] [2]
Ilp3 **Insulin-like peptide 3** (CG14167)	IGF1 IGF2 INS	Partial genetic ablation of the neurosecretory Ilp-producing cells that reside in the brain and are the primary producers of Ilp2, Ilp3 and Ilp5 in the adult body resulted in median lifespan increase by 10.5% in males and 18.5% and 33.5% in virgin and mated females, respectively.	[2]
Ilp4 **Insulin-like peptide 4** (CG6736)	INSL3	-	-
Ilp5 **Insulin-like peptide 5** (CG33273)	INS INS-IGF2	Partial genetic ablation of the neurosecretory Ilp-producing cells that reside in the brain and are the primary producers of Ilp2, Ilp3 and Ilp5 in the adult body resulted in median lifespan increase by 10.5% in males and 18.5% and 33.5% in virgin and mated females, respectively.	[2]
Ilp6 **Insulin-like peptide 6** (CG14049)	IGF1 IGF2	-	-
Ilp7 **Insulin-like peptide 7** (CG13317)	-	-	-
InR **Insulin-like receptor** (CG18402)	IGF1R INSR INSRR LMTK2	Females of transheterozygous *InR* flies are 85% longer lived than wild-type controls. Other homo- and transheterozygous *InR* mutants were found to be strongly or moderately short-lived. The heterozygote $InR^{E19(HR)}/InR^{+(HR)}$ does not extend lifespan. Other transheterozygous and hemizygous *InR* mutants strongly or moderately extended lifespan. There was no difference in lifespan between flies	[3] [4] [5]

		with cardiac-specific overexpression of *InR* and flies with cardiac-specific overexpression of *Pten*. Activation of InR expression in intestinal stem cells and enteroblasts results in 6% and 10% reduction of mean lifespan in males and females, respectively, compared with control. Induced inhibition of InR in intestine using dominant-negative InR causes 7% extension of mean lifespan compared with uninduced flies.	 [6]
Chico (CG5686)	IRS1 IRS2 IRS4	Heterozygous *chico* males and females showed increase of median adult lifespan of 13% and 36%, respectively. Homozygous *chico* females exhibited an increase of median and maximum lifespan of up to 48% and 41%, respectively. Heterozygous *chico* males and females showed increase of lifespan of 51% and 37%, respectively. Homozygous *chico* females and males showed increase of lifespan of 59% and 6%, respectively.	[7] [8]
Lnk (CG17367)	SH2B2 SH2B1 SH2B3	Heterozygous *Lnk* flies did not show any significant differences in lifespan. Homozygous *Lnk* females and males showed increase of median lifespan of approximately 11% and 15%, respectively.	[9]
Pi3K21B (CG2699)	PIK3R3 PIK3R2 PIK3R1 LOC110117 498-PIK3R3	-	-
Pi3K92E **Phosphatidylinositol 3-kinase 92E** (CG4141)	PIK3CD PIK3CB PIK3CA PIK3CG	Overexpression of dominant-negative Pi3K92E in intestinal stem cells and enteroblasts results in 3% and 5% reduction of mean lifespan in males and females, respectively, compared with control. Induced inhibition of Pi3K92E in intestine using dominant-negative Pi3K92E causes 7% extension of mean lifespan compared with uninduced flies.	[6]
Pten **Phosphatase and tensin homolog** (CG5671)	PTEN TPTE2 TPTE	*Pten* overexpression in adult head fat body increased the median lifespan of male and female flies of 19% and 17%, respectively. *Pten* overexpression in fat body had no significant effect on lifespan. *Pten* overexpression in muscles extends the median lifespan of males of 20%. There was no difference in lifespan between flies with cardiac-specific overexpression of *InR* and flies with cardiac-specific overexpression of *Pten*.	[10] [11] [5]
Pdk1 **Phosphoinositide-dependent kinase 1** (CG1210)	PDPK1 PDPK2P	-	-
Akt **Akt kinase** (CG4006)	AKT2 AKT3 AKT1 SGK1	Inhibition of Akt expression in intestinal stem cells and enteroblasts results in 11% and 7% reduction of mean lifespan in males and females, respectively, compared with control. Induced	[6]

	SGK2 C8orf44-SGK3	inhibition of Akt in intestine using RNAi causes more than 10% extension of mean lifespan compared with uninduced flies.	
Foxo **Forkhead box, sub-group O** (CG3143)	FOXO3 FOXO1 FOXO4	Heterozygous *foxo* males and females showed decrease of mean lifespan of about 5% and increase of mean lifespan of 29%, respectively.	[12]
		Overexpression of *foxo* in adult head fat body increased the median lifespan of male and female flies of about 24% and 16%, respectively. Pan-neuronal overexpresion of *foxo* as well as its overexpression in fat body, neurolemma and glial cells had no significant effect on lifespan.	[10]
		Overexpression of *foxo* in muscles extends the median lifespan of male flies of about 23%.	[11]
		Induced expression of *foxo* in the adult fat body increased lifespan of female flies by 20 to 50%.	[13]
		Heterozygosity for $foxo^{21}$ or $foxo^{25}$ does not affect life span in wild-type backgrounds.	[14]
		Activation of Foxo expression in intestinal stem cells and enteroblasts results in 6% and 4% reduction of mean lifespan in males and females, respectively, compared with control.	[6]
14-3-3ε (CG31196)	YWHAE	Heterozygous *14-3-3ε* males and females showed increase of mean lifespan of about 61% and 21%, respectively.	[12]
14-3-3ζ (CG17870)	YWHAZ YWHAB YWHAG YWHAH SFN YWHAQ	-	-

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