Supplementary Table 4. Summary of input signals and chromatin effector proteins for JNK 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)
Egr **Eiger** (CG12919)	EDA TNFSF12-TNFSF13 TNFSF13B TNFSF13 TNFSF12	*egr* mutant flies displayed of about 40% increase in lifespan compared to wild-type flies.	[1]
Wgn **Wengen** (CG6531)	NGFR TNFRSF4	-	-
Grnd **Grindelwald** (CG10176)	-	-	-
CYLD **Cylindromatosis** (CG5603)	CYLD	*CYLD* mutant flies show about 42% reduction of lifespan as compared with wild-type or heterozygous *CYLD* flies. This reduction was largely rescued by one copy of *CYLDRes* and fully rescued by ubiquitous expression of *Bsk*.	[2]
Traf6 **TNF-receptor-associated factor 6** (CG10961)	TRAF6 TRAF5 TRAF7	Knock-down of *Traf6* in intestinal cells causes about 24% reduction of mean longevity compared with control.	[3]
Traf4 **TNF-receptor-associated factor 4** (CG3048)	TRAF4 TRAF1 TRAF2 TRAF3 TRAF5 TRAF7	-	-
Msn **Misshapen** (CG16973)	TNIK MINK1 MAP4K4 NRK	RNAi of *msn* decreased lifespan in about 11days in female flies compared to control. Overexpression of *msn* in eye and antennal imaginal disks causes about 70% reduction of lifespan compared with control.	[4] [5]
Tak1 **TGF-β activated kinase 1** (CG18492)	MAP3K7 RIPK1 RIPK3 ANKK1 DSTYK FPGT-TNNI3K RIPK4 TNNI3K	Knock-down of *Tak1* in intestinal cells causes about 5% extension of mean longevity compared with control.	[3]
Tab2 **TAK1-associated binding protein 2** (CG7417)	TAB2 TAB3 TNFRSF1A	-	-
Slpr **Slipper** (CG2272)	MAP3K9 MAP3K10 MAP3K11 MAP3K21 RIPK1	Misexpression of *slpr* in muscles and salivary glands or in hemocytes causes 79% or 71% reduction in mean longevity, respectively, compared with control.	[6]

		RIPK2 ANKK1 DSTYK FPGT-TNNI3K RIPK4 TNNI3K		
Ask1 **Apoptotic signal-regulating kinase 1** (CG4720)		MAP3K15 MAP3K5 MAP3K3	-	-
Mekk1 (CG7717)		MAP3K4 MAP3K2 MAP3K3 MAP3K19	-	
Wnd **Wallenda** (CG8789)		MAP3K13 MAP3K12	-	-
Mkk4 **MAP kinase kinase 4** (CG9738)		MAP2K4 LOC100996792	-	-
Hep **Hemipterous** (CG4353)		MAP2K7 LOC100996792	Neuronal overexpression of *hep* extended lifespan of about 25% compared to control. Activation of *hep* expression in intestinal stem cells and enteroblasts results in about 6% reduction of mean lifespan in male and female flies compared with control. Overexpression of *hep* in intestinal stem cells and enteroblasts causes 51% and 25% reduction of mean lifespan in male and female flies, respectively, compared to control.	[7] [8] [9]
STRIATIN-INTERACTING PHOSPHATASE AND KINASE COMPLEX STRIPAK (FBgg0000915)	**Ccm3** **Cerebral cavernous malformation 3** (CG5073)	PDCD10	-	-
	Cka **Connector of kinase to AP-1** (CG7392)	STRN3 STRN STRN4	-	-
	Fgop2 **Fibroblast growth factor receptor 1 oncogene partner 2** (CG10158)	FGFR1OP2 SIKE1	-	-
	Mob4 **MOB kinase activator 4** (CG3403)	MOB4 HSPE1-MOB4	-	-
	Mts **Microtubule star**	PPP2CA PPP2CB PPP5D1	-	-

	(CG7109)			
	Naus Nausicaa (CG10915)	CTTNBP2NL CTTNBP2 FILIP1L FILIP1 LUZP1	-	-
	Pp2A-29B Protein phosphatase 2A at 29B (CG17291)	PPP2R1A PPP2R1B PPP4R4 PPP4R1 RELCH	-	-
	Slmap Sarcolemma associated protein (CG17494)	SLMAP CCDC136 TRAF3IP3 RNF8	-	-
	Strip Striatin interacting protein (CG11526)	STRIP1 STRIP2	-	-
Src42A **Src oncogene at 42A** (CG44128)		FRK PTK6 SRMS	-	-
Src64B **Src oncogene at 64B** (CG7524)		FYN SRC YES1 FGR BLK HCK LCK LYN PTK6 SRMS SLA2 SLA	-	-
Btk **Bruton tyrosine kinase** (CG8049)		TEC TXK ITK BTK BMX PTK6 SRMS	The *Btk* mutation reduced adult longevity to 11% of wild-type. Overexpression of Btk during the late larval and pupal stages prolonged the adult lifespan of *Btk* mutants to 53% and 76% of the wild-type level.	[10]
Dok **Downstream of kinase** (CG2079)		DOK2 DOK1 DOK3 DOK4 DOK5 DOK6 DOK7	-	-
Shark **SH2 ankyrin repeat kinase** (CG18247)		ZAP70 SYK	-	-
Rac1 (CG2248)		RAC1 RAC2 RAC3 RHOBTB3	Knockdown of *Rac1* in neurons did not affect life span.	[11]

	RHOF RND1 RND2 RND3		
Puc **Puckered** (CG7850)	DUSP10 DUSP8 DUSP16 DUSP1 DUSP4 DUSP2 DUSP5 EPM2A STYXL1	Heterozygosity of two *puc* loss-of-function alleles showed a significantly longer lifespan (of about 48% and 62%) than wild-type flies. This phenotype was reduced in puc^{E69} heterozygotes in a hep^{1} hemizygous backgound. Long-lived phenotype in *puc* mutants can be reverted to wild-type levels in the back-ground of *foxo* loss-of-function allele heterozygotes	[7] [12]
Prx2 **Peroxiredoxin 2** (CG1633)	PRDX2 PRDX1	Neuronal overexpression of *Prx2* in neurons increased lifespan of about 13% compared to wild-type flies. Neuronal knockdown of *Prx2* as well as the loss-of-function mutation caused about 8% and 14% reduction in lifespan, respectively. Induced expression of *Prx2* in adult neurons extended lifespan by 26% in females and 29% in males compared with the control. Overexpression of *Prx2* in intestinal stem cells results in 12% and 20% extension of mean lifespan in male and female flies, respectively, compared with control.	[13] [8]
Bsk **Basket** (CG5680)	MAPK8 MAPK10 MAPK9	Strong inhibition of *bsk* expression in intestinal stem cells and enteroblasts results in 16% and 10% reduction of mean lifespan in male and female flies, respectively, compared with control. Induced inhibition of *bsk* in intestine using RNAi and dominant-negative Bsk causes 12% and 14% extension of mean lifespan, respectively, compared with uninduced flies.	[8]
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. 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. Overexpression of *foxo* in muscles extends the median lifespan of male flies of about 23%. Induced expression of *foxo* in the adult fat body increased lifespan of female flies by 20 to 50%. Heterozygosity for $foxo^{21}$ or $foxo^{25}$ does not affect life span in wild-type backgrounds. 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.	[14] [15] [16] [17] [12] [8]

AP-1 transcription factor	**Kay Kayak** (CG33956)	FOS FOSL1 FOSL2 FOSB	*P*-element mutation in the *kay* gene was associated with increased lifespan.	[18]
	Jra Jun-related antigen (CG2275)	JUND JUN JUNB	Reduction of *Jra* activity in the whole animal or in the gut in the absence of infection does not affect lifespan, suggesting that Jra is haplo-sufficient in this context.	[19]
Stat92E Signal-transducer and activator of transcription protein at 92E (CG4257)		STAT5B STAT5A STAT6 STAT1 STAT2 STAT3 STAT4	Stat92E mutation exhibited shortened lifespans compared with wild-type control flies of about 20%.	[20]

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