Supplementary Table S3. Summary of input signals and chromatin effector proteins for NF-kB 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)
Spz **Spatzle** (CG6134)	-	Downregulation of *spz* does not influence lifespan. Heterozygous loss-of-function *spz* mutants extended median longevity by 25 and 30%, respectively.	[1] [2]
Tl **Toll** (CG5490)	TLR1 TLR2 TLR3 TLR4 TLR5 TLR6 TLR7 TLR9 TLR10 IL1RAPL2	Downregulation of *Tl* extended lifespan for about 12% and 2% in female and male flies, respectively.	[1]
Pli **Pellino** (CG5212)	PELI1 PELI2 PELI3	-	-
Myd88 (CG2078)	MYD88 SIGIRR TIRAP	-	-
Tub **Tube** (CG10520)	HASPIN IRAK4	-	-
Pll **Pelle** (CG5974)	IRAK4 IRAK1 IRAK2 IRAK3 ANKK1 MIR718 MIR6502 PKDCC RIPK4	-	-
Cact **Cactus** (CG5848)	NFKBIA NFKBIB NFKBIE ANKRD22 BCL3	Silencing the antagonist *cact* leads to about 45% reduction of lifespan in females and males. Knockdown of *cact* pan-neuronally resulted in a dramatic reduction in the median lifespan of male and female flies for about 30% and 20%, respectively. Knockdown of *cact* in insulin-specific cells reduced median lifespan of male and female flies for about 30% and 15%, respectively. Neuroblast-specific *cact* overexpression influenced the median lifespan of male and female flies for about 16% and 4%,	[1] [3]

		respectively, suggesting a possible sex-specific effect on lifespan.	
Dif **Dorsal-related immunity factor** (CG6794)	RELA RELB	Pan-neuronal *Dif* overexpression leads to 25% reduction of median lifespan in male and female flies. Overexpression of *Dif* in insulin-specific cells leads about 12% and 25% reduction in median lifespan of male and female flies, respectively. Neuroblast-specific *Dif* overexpression leads to 18% reduction of median lifespan in male flies and does not influence lifespan in females.	[3]
Dl **Dorsal** (CG6667)	RELA REL	-	-
PGRP-LC **Peptidoglycan recognition protein LC** (CG4432)	PGLYRP1 PGLYRP3 PGLYRP4	Overexpression of *PGRP-LC* in muscles leads to 40% and 36% reduction of the average lifespan in males and females, respectively. Overexpression of *PGRP-LC* in the fat body leads to about 90% and 84% reduction of the average lifespan in males and females, respectively.	[4]
PGRP-LE **Peptidoglycan recognition protein LE** (CG8995)	PGLYRP1 PGLYRP3 PGLYRP4 ADIPOQ	Overexpression of *PGRP-LE* in the abdominal fat body leads to about 22% and 3% reduction of the lifespan in males and females, respectively.	[5]
Pirk **Poor Imd response upon knock-in** (CG15678)	-	*pirk* mutant flies showed a 9.1% reduction in maximum lifespan compared with wild-type controls.	[6]
Imd **Immune deficiency** (CG5576)	-	Downregulation of *imd* leads to about 15% and 12% increase of mean lifespan in heterozygous males and females, respectively, and to 23% and 22% increase of mean lifespan in homozygous males and females, respectively.	[7]
Diap2 **Death-associated inhibitor of apoptosis 2** (CG8293)	BIRC2 BIRC3 XIAP BIRC7 BIRC8 NAIP F11 F12 NLRC4	-	-
Eff **Effete** (CG7425)	UBE2D2 UBE2D3 UBE2D1 UBE2D4 UBE2DNL UBE2J1 UBE2T UBE2U	-	-
Ben **Bendless** (CG18319)	UBE2N UBE2NL UBE2J1 UBE2T UBE2U	*ben* mutant males show reduction of lifespan for about 22% as compared with wild-type males. This reduction could be rescued by neural expression of *hep*.	[8]

Uev1A **Ubiquitin-conjugating enzyme variant 1A** (CG10640)	UBE2V2 TMEM189-UBE2V1 UBE2V1	-	-
Dredd **Death related ced-3/Nedd2-like caspase** (CG7486)	CASP10 CASP8 CASP9 CFLAR CASP1 CARD8 PEA15	Hypomorphic *Dredd* mutation leads to 12% increase of the lifespan compared to controls. *Dredd*-null flies had a 8% reduction in lifespan compared with their genetic backgrounds. RNAi of *Dredd* had sexually antagonistic effects on lifespan, leading to 10 days increase and 15 days decrease of lifespan compared to control in male and female flies, respectively.	[6] [9]
Fadd **Fas-associated death domain** (CG12297)	FADD	-	-
Trbd **Trabid** (CG9448)	ZRANB1 OTUD7A OTUD7B TNFAIP3 VCPIP1	*trbd* mutant flies showed 37.1% reduction in maximum lifespan compared with wild-type controls. 50% of flies heterozygous for both *pirk* and *trbd* survived the 30-day mark (LT 50 = 32). A similar effect was observed in flies deficient for *pirk* in a *trbd* heterozygous background (LT 50 = 27). Just deleting *trbd* (in a *pirk* heterozygous background) had serious consequences, as 50% of flies were dead by 18 days (LT 50 = 18). More significantly however, the double mutant *pirk*; *trbd* had a dramatic reduction in life span compared to either single mutant (+/*pirk*; *trbd* or *pirk*; +/*trbd*) or double heterozygote (+/*pirk*; +/*trbd*) since 50% of flies were dead before the 14-day mark (LT 50 = 14). This phenomenon was suppressed in *dredd*; *pirk*; *trbd* flies (LT 50 = 37) where IMD was inactive.	[6] [10]
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.	[11]
Tab2 **TAK1-associated binding protein 2** (CG7417)	TAB2 TAB3 TNFRSF1A	-	-
Key **Kenny** (CG16910)	IKBKG OPTN CEP55 TNIP2	-	-
IKKβ **I-kappaB kinase β** (CG4201)	CHUK IKBKB IKBKE ERLIN1	-	-

Casp **Caspar** (CG8400)	FAF1	*casp* mutants have shorter lifespans than the controls, with the change in median lifespan being shorter by 19%.	[12]
Rel **Relish** (CG11992)	NFKB1 NFKB2	Pan-neuronal *Rel* overexpression leads in 25% reduction of median lifespan in male and female flies. *Rel* overexpression in insulin-producing cells and neuroblasts leads about 1% and 11% reduction of the lifespan of male and female flies, respectively. Pan-neuronal overexpression of the constitutively-active Rel domain of Rel reduced the median lifespan for about 25% in males and females. Overexpression of the constitutively-active Rel domain of Rel in insulin-producing cells leads reduction of median lifespan for about 20% in male and female flies. Overexpression of the constitutively-active Rel domain of Rel in neuroblasts leads reduction of median lifespan for about 15% and 9% in male and female flies, respectively. *Rel*-null flies had a statistically significant reduction (for about 23%) in lifespan compared with their genetic backgrounds. RNAi-dependent silencing of *Rel* in glia, neurons and intestine resulted in about 60%, 38% and 35% increase of lifespan, respectively. Ubiquitous overexpression of *Rel* shortened lifespan for about 30% and 39% in female and male flies, respectively. Overexpression of *Rel* in fat body shortened lifespan for about 24% and 18% in female and male flies, respectively. Underexpression of *Rel* shortened lifespan of females for about 4% and extended lifespan of males for about 3%. Underexpression of *Rel* in fat body extended lifespan for about 11% and 13% in female and male flies, respectively	[3] [6] [13]
Tg **Transglutaminase** (CG7356)	TGM1 TGM4 F13A1 TGM2 TGM5 EPB42 TGM3 TGM6 TGM7 CCNI	*Tg* mutant flies showed a 24.2% reduction in maximum lifespan compared with wild-type controls.	[6]
Charon (CG5118)	ANKRD7 ANKRD26P1 ASB7 ASB15 ASB18 BCL3 NFKBIE POTEA POTEB2 POT EB3	Long-term GeneSwitch-mediated depletion of pickle in enteroblasts and enterocytes caused a significant reduction in median lifespan (6-10%).	[14]

	POTEB POTEC POTED POTEE POTEF POTEG POTEH POTEI POTEJ POTEM		
Zfh1 **Zn finger homeodomain 1** (CG1322)	ZEB2 ZEB1	-	-
Nub **Nubbin** (CG34395)	POU2F1 POU2F2 POU5F1B POU5F1 POU5F2 CCHCR1	Importantly, *nub* mutant flies exhibited a considerably reduced lifespan (T_{50} = 21.7 days) compared to OregonR (T_{50} = 68.5 days).	[15]
Cad **Caudal** (CG1759)	CDX2 CDX1 CDX4 URAD	There was no significant increase (but a minor reduction) in the longevity of flies with *cad* depletion compared to the control flies.	[16]
Polybromo (CG11375)	PBRM1	-	-
Akirin (CG8580)	AKIRIN2 AKIRIN1	-	-
Gcn5 **Gcn5 acetyltransferase** (CG4107)	KAT2A KAT2B	-	-

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