**Supplementary Table S2.** Summary of input signals and chromatin effector proteins for TOR 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)** |
|---|---|---|---|---|
| **Slif**<br>**Slimfast**<br>(CG11128) | | SLC7A1<br>SLC7A3<br>SLC7A2 | - | - |
| **Sesn**<br>**Sestrin**<br>(CG11299) | | SESN3<br>SESN1<br>SESN2 | *Sesn* mutant flies have median lifespan reduced by 13% on the 1.0× yeast food, compared with controls. Ubiquitous overexpression of *Sesn* significantly increased lifespan with a median extension of 10%. Overexpression of *Sesn* in neurons, fat bodies and enterocytes did not cause lifespan extension. In contrast, overexpression of *Sesn* in intestinal stem cells resulted in a significant lifespan extension, again with a median lifespan extension of ~10%. | [1] |
| **GATOR2 complex** | **Mio**<br>**Missing oocyte**<br>(CG7074) | MIOS | - | - |
| | **Nup44A**<br>**Nucleoporin at 44A**<br>(CG8722) | SEH1L | - | - |
| | **Sec13**<br>**Secretory 13**<br>(CG6773) | SEC13 | - | - |
| | **Wdr24**<br>**WD repeat domain 24**<br>(CG7609) | WDR24 | - | - |
| | **Wdr59**<br>**WD repeat domain 59**<br>(CG4705) | WDR59 | - | - |
| **GATOR1 complex** | **Iml1**<br>**Increased minichromosome loss 1**<br>(CG12090) | DEPDC5 | - | - |
| | **Nprl2**<br>**Nitrogen permease regulator-like 2**<br>(CG9104) | NPRL2 | The median lifespan of *Nprl2* null mutants (34 d) was markedly shorter than that of wild-type flies (64 d). | [2] |
| | **Nprl3**<br>**Nitrogen permease regulator-like 3**<br>(CG8783) | NPRL3 | - | - |
| **RAGULATOR** | **Lamtor1**<br>**Late** | LAMTOR1 | - | - |

| | | | | |
|---|---|---|---|---|
| **complex** | **endosomal/lysosomal adaptor, MAPK and MTOR activator 1** (CG14184) | | | |
| | **Lamtor2 Late endosomal/lysosomal adaptor, MAPK and MTOR activator 2** (CG5189) | LAMTOR2 | - | - |
| | **Lamtor3 Late endosomal/lysosomal adaptor, MAPK and MTOR activator 3** (CG5110) | LAMTOR3 | - | - |
| | **Lamtor4 Late endosomal/lysosomal adaptor, MAPK and MTOR activator 4** (CG14977) | LAMTOR4 | - | - |
| | **Lamtor5 Late endosomal/lysosomal adaptor, MAPK and MTOR activator 5** (CG14977) | LAMTOR5 | - | - |
| **VACUOLAR ATPASE SUBUNITS** (FBgg0000111) | **ATP6AP2 ATPase H+ transporting accessory protein 2** (CG8444) | ATP6AP2 | - | - |
| | **CG5421** | ATP6AP1 ATP6AP1L | - | - |
| | **VhaAC45 Vacuolar H+ ATPase AC45 accessory subunit** (CG8029) | ATP6AP1 ATP6AP1L | - | - |

| | | | | |
|---|---|---|---|---|
| | **VhaAC45RP VhaAC45-related protein** (CG31030) | ATP6AP1 ATP6AP1L | Knock-down of *VhaAC45RP* expression in neurons decreases adult longevity. Pan-neuronal expression of *VhaAC45RP$^{RNAi3}$* and Dcr-2 led to a marked shortening of the lifespan of adult flies. | [3] |
| | **Vha16-1 Vacuolar H+ ATPase 16kD subunit 1** (CG3161) | ATP6V0C | - | - |
| | **Vha16-2 Vacuolar H+ ATPase 16kD subunit 2** (CG32089) | ATP6V0C | - | - |
| | **Vha16-3 Vacuolar H+ ATPase 16kD subunit 3** (CG32090) | ATP6V0C | - | - |
| | **Vha16-4 Vacuolar H+ ATPase 16kD subunit 4** (CG9013) | ATP6V0C | - | - |
| | **Vha16-5 Vacuolar H+ ATPase 16kD subunit 5** (CG9013) | ATP6V0C | - | - |
| | **Vha100-1 Vacuolar H+ ATPase 100kD subunit 1** (CG1709) | ATP6V0A1 ATP6V0A4 ATP6V0A2 MIR5010 | - | - |
| | **Vha100-2 Vacuolar H+ ATPase 100kD subunit 2** (CG18617) | ATP6V0A4 ATP6V0A1 ATP6V0A2 | - | - |
| | **Vha100-3 Vacuolar H+ ATPase 100kD subunit 3** (CG30329) | ATP6V0A1 ATP6V0A2 ATP6V0A4 TCIRG1 | - | - |
| | **Vha100-4 Vacuolar H+ ATPase** | ATP6V0A4 ATP6V0A2 TCIRG1 | - | - |

| | | | | |
|---|---|---|---|---|
| | **100kD subunit 4** (CG7678) | | | |
| | **Vha100-5 Vacuolar H+ ATPase 100kD subunit 5** (CG12602) | ATP6V0A1 ATP6V0A4 ATP6V0A2 | - | - |
| | **VhaAC39-1 Vacuolar H+ ATPase AC39 subunit 1** (CG2934) | ATP6V0D1 ATP6V0D2 | Gut-specific and systemic *VhaAC39-1* RNAi lines showed the shortening of median lifespan of flies by 63% and 9%, respectively, in comparison with the control. Oerexpression of *VhaAC39-1* did not affect the longevity of flies. Additionally, a lifespan assay in an independent *VhaAC39-1* RNAi line showed that the median lifespan of gut-specific and systemic *VhaAC39-1* RNAi flies was shortened by 68% and 49%, respectively. | [4] |
| | **VhaAC39-2 Vacuolar H+ ATPase AC39 subunit 2** (CG4624) | ATP6V0D1 ATP6V0D2 | - | - |
| | **VhaM9.7-a Vacuolar H+ ATPase M9.7 subunit a** (CG1268) | ATP6V0E1 ATP6V0E2 | - | - |
| | **VhaM9.7-b Vacuolar H+ ATPase M9.7 subunit b** (CG7625) | ATP6V0E1 ATP6V0E2 | - | - |
| | **VhaM9.7-c Vacuolar H+ ATPase M9.7 subunit c** (CG11589) | ATP6V0E1 ATP6V0E2 | - | - |
| | **VhaM9.7-d Vacuolar H+ ATPase M9.7 subunit d** (CG14909) | ATP6V0E1 ATP6V0E2 | - | - |
| | **VhaPPA1-1 Vacuolar H+ ATPase PPA1 subunit 1** (CG7007) | ATP6V0B | - | - |
| | **VhaPPA1-2 Vacuolar H+ ATPase PPA1** | ATP6V0B | - | - |

| | | | | |
|---|---|---|---|---|
| | **subunit 2** (CG7026) | | | |
| | **Vha68-1 Vacuolar H+ ATPase 68kD subunit 1** (CG12403) | ATP6V1A | - | - |
| | **Vha68-2 Vacuolar H+ ATPase 68kD subunit 2** (CG3762) | ATP6V1A | - | - |
| | **Vha68-3 Vacuolar H+ ATPase 68kD subunit 3** (CG5075) | ATP6V1A | - | - |
| | CG15719 | ATP6V1F | - | - |
| | **Vha13 Vacuolar H+ ATPase 13kD subunit** (CG6213) | ATP6V1G1<br>ATP6V1G2<br>ATP6V1G3<br>ATP6V1G2-DDX39B | - | - |
| | **Vha14-1 Vacuolar H+ ATPase 14kD subunit 1** (CG8210) | ATP6V1F | - | - |
| | **Vha14-2 Vacuolar H+ ATPase 14kD subunit 2** (CG1076) | ATP6V1F | - | - |
| | **Vha26 Vacuolar H+-ATPase 26kD subunit** (CG1088) | ATP6V1E1<br>ATP6V1E2 | - | - |
| | **Vha36-1 Vacuolar H+ ATPase 36kD subunit 1** (CG8186) | ATP6V1D | - | - |
| | **Vha36-2 Vacuolar H+ ATPase 36kD subunit 2** (CG13167) | ATP6V1D | - | - |

| | | | | |
|---|---|---|---|---|
| | **Vha36-3**<br>**Vacuolar H+ ATPase 36kD subunit 3**<br>(CG8310) | ATP6V1D | - | - |
| | **Vha44**<br>**Vacuolar H+ ATPase 44kD subunit**<br>(CG8048) | ATP6V1C1<br>ATP6V1C2 | - | - |
| | **Vha55**<br>**Vacuolar H+-ATPase 55kD subunit**<br>(CG17369) | ATP6V1B2<br>ATP6V1B1<br>RHO | - | - |
| | **VhaSFD**<br>**Vacuolar H+-ATPase SFD subunit**<br>(CG17332) | ATP6V1H | - | - |
| **RagA-B**<br>**Ras-related GTP binding A/B**<br>(CG11968) | | RRAGB<br>RRAGA<br>IL4 | - | - |
| **RagC-D**<br>**Ras-related GTP binding C/D**<br>(CG8707) | | RRAGC<br>RRAGD | - | - |
| **Lkb1**<br>**Lkb1 kinase**<br>(CG9374) | | STK11 | Ubiquitous overexpression of *Lkb1* in females leads to 6.5% increase of mean lifespan relative to control. No significant increase in lifespan was observed in male flies. | [5] |
| **AMPK complex** | **Alc**<br>**Alicorn**<br>(CG8057) | PRKAB1<br>PRKAB2 | - | - |
| | **AMPKα**<br>**AMP-activated protein kinase α subunit**<br>(CG3051) | PRKAA2<br>PRKAA1 | *AMPKα*-RNAi leads in approximately 20% decrease in lifespan compared to wild-type flies. | [6] |
| | **SNF4Aγ**<br>**SNF4/AMP-activated protein kinase gamma subunit**<br>(CG17299) | PRKAG1<br>PRKAG2<br>PRKAG3 | - | - |
| **WDB-PP2A complex** | **Mts**<br>**Microtubule star**<br>(CG7109) | PPP2CA<br>PPP2CB | - | - |
| | **Wdb**<br>**Widerborst** | PPP2R5E<br>PPP2R5A | Ubiquitous overexpression of *wdb* leads to 17% and 13% increase in mean lifespan of males and | [5] |

| | | | | |
|---|---|---|---|---|
| | (CG5643) | PPP2R5B | females, respectively. | |
| | **Pp2A-29B Protein phosphatase 2A at 29B** (CG17291) | PPP2R1A<br>PPP2R1B<br>PPP4R4<br>PPP4R1<br>RELCH | - | - |
| **Chrb**<br>**Charybde**<br>(CG7533) | | DDIT4L<br>DDIT4 | - | - |
| **Scyl**<br>**Scylla**<br>(CG7590) | | DDIT4<br>DDIT4L | - | - |
| **Gig**<br>**Gigas**<br>**(**CG6975**)** | | TSC2 | Overexpression of *gig* under ubiquitously expressed driver extended mean lifespan at 29°C by 12%. Overexpression of *gig* in the eye or in the nervous system did not extend lifespan. Overexpression of *gig* by using the drivers that are predominantly expressed in the muscle and fat, resulted in mean lifespan extensions of 27% and 37%, respectively, at 29°C. The fat-specific drivers, when used to overexpress *gig*, also led to a mean lifespan extension of 22% and 31%, respectively, at 29°C. | [7] |
| **Tsc1**<br>**(**CG6147**)** | | TSC1 | Overexpression of *Tsc1* under ubiquitously expressed driver extended mean lifespan at 29°C by 14%. | [7] |
| **Rheb**<br>**Ras homolog enriched in brain**<br>**(**CG1081**)** | | RHEB<br>RHEBL1 | Overexpression of *Rheb* in enteroblasts shortened mean lifespan by 15%. Overexpression of *Rheb* in midgut stem and progenitor cells shortened the lifespan and mean lifespan by 33%. | [8] |
| **Fkbp12**<br>**FK506-binding protein 12kD**<br>(CG11001) | | FKBP1A<br>FKBP1B<br>FKBP1C | - | - |
| **Tor**<br>**Target of rapamycin**<br>**(**CG5092**)** | | MTOR<br>PRKDC | Ubiquitous overexpression of dominant-negative form of *Tor* leads to 24% and 26% increase in mean lifespan increase at 29°C and at 25°C, respectively. Overexpression of the dominant-negative form of *Tor* by using the fat-specific driver leads to 30% increase in mean lifespan at 29°C.<br><br>The median lifespan of the heteroallelic $Tor^{2L7}/Tor^{k17004}$ mutants was increased by 20% under normal feeding conditions. Complete loss of *Tor* function results in early larval lethality. | [7]<br><br>[9] |
| **Lst8**<br>(CG3004) | | MLST8 | - | - |
| **Raptor**<br>(CG4320) | | RPTOR | Muscle-specific knockdown of *raptor* leads to late pupal lethality in *Drosophila* due to an inability to eclose from the pupal case. And a large proportion of the flies that successfully eclosed died shortly afterwards. However, among the flies that survived, they generally had a normal lifespan. | [10] |
| **Rictor**<br>**rapamycin-insensitive companion of Tor**<br>(CG8002) | | RICTOR | Cardiac-specific overexpression of *rictor* leads to 12% extension of mean lifespan. | [11] |

| | | | | |
|---|---|---|---|---|
| **Sin1**<br>**SAPK-interacting protein 1**<br>(CG10105) | | MAPKAP1 | - | - |
| **Mitf**<br>(CG43369) | | MITF<br>TFEB<br>TFE3<br>TFEC | *Mitf* overexpression in the nervous system led to 10 and 11% decrease in the average and median lifespan of females, respectively. | [12] |
| **REPTOR**<br>**Repressed by TOR**<br>(CG13624) | | CREBRF | *REPTOR* knockout leads in about 59% and 40% decrease in lifespan in male and female flies, respectively. | [13] |
| **REPTOR-BP**<br>**REPTOR-binding partner**<br>(CG18619) | | CREBL2<br>ALOX15B | *REPTOR-BP* knockout leads in about 40% and 45% decrease in lifespan in male and female flies, respectively. | [13] |
| **Maf1**<br>**(**CG40196) | | MAF1 | Gut-specific overexpression of *Maf1* mildly extended lifespan for about 2%. | [14] |
| **Myc**<br>(CG10798) | | MYC<br>MYCL<br>MYCN<br>MXD1<br>MXD4<br>MYCLP1 | *Myc* overexpression shortened median lifespan from 38 days in controls to 22 days at 29°C and from a median of 58 days in controls to 31 days at 25°C. *Myc* haploinsufficiency extends a median lifespan from 59 to 67days. | [15] |
| **Nclb**<br>**No child left behind**<br>(CG6751) | | PWP1 | - | - |
| **Tif-IA**<br>(CG3278) | | RRN3<br>RRN3P1<br>RRN3P2 | The longevity of females harboring allele *Tif-IA$^{KG}$*, which abolishes almost completely the *Tif-IA* expression, was robustly observed in three independent experimental trials with an average 8% extension of the median lifespan. | [16] |
| **Pol I***<br>12 genes<br>(FBgg0001647) | **Polr1A**<br>**RNA polymerase I subunit A**<br>(CG10122) | POLR1A | *Polr1A$^{SH/+}$* females have about 12% extension of the lifespan. | [16] |
| **Pol III***<br>17 genes<br>(FBgg0001648) | **Polr3D**<br>**RNA polymerase III subunit D**<br>(CG5147) | POLR3D | Partial reduction in *Polr3D* mRNA in the adult fly gut leads to slightly extension of lifespan for approximately 5%. | [14] |

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