Chapter 8
Genes and Pathways That Influence Longevity in *Caenorhabditis elegans*

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Abstract The roundworm *Caenorhabditis elegans* is one of the most popular model organisms for research on aging because of its short lifespan and genetic tractability. Studies using *C. elegans* have identified many genes and pathways that regulate aging, several of which are conserved in other species, including mammals. In this chapter, we describe longevity-regulatory pathways including insulin/IGF-1 (insulin-like

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growth factor 1) signaling, TOR (target of rapamycin) signaling, autophagy, mitochondrial respiration, and HIF-1 (hypoxia-inducible factor 1) pathways. We also review the effects of dietary restriction, a key environmental factor that influences aging, on longevity-regulatory genetic factors. In addition, we illustrate the roles of two important *C. elegans* tissues, those of the sensory neural and reproductive systems, in regulating longevity at the molecular level. For each of the subtopics, we explain how changes in the expression of genes involved in each pathway and system alter longevity. We also speculate on the evolutionary significance of the genes and pathways that affect longevity. Given the conserved nature of longevity regulation, the dissection of the roles of these genetic factors in determining the *C. elegans* lifespan will provide important clues for understanding the secrets of human aging.

Keywords *C. elegans* • Aging • Insulin/IGF-1 • Target of rapamycin • Dietary restriction • Autophagy • Hypoxia-inducible factor • Mitochondria • Sensory neurons • Reproductive system

8.1 Introduction

For a long time, the lifespans of living organisms were believed to be limited by the passive, age-dependent degeneration of tissues, which eventually leads to death. However, the findings of studies conducted in the past two decades tell us otherwise. Scientists have shown that organismal lifespans are subjected to active regulation by many genes and pathways. Although the exact mechanisms remain unclear, we now know that genetic factors influence the rate of organismal aging, in response to changes in environmental signals as well as physiologic inputs.

The small roundworm *Caenorhabditis elegans* has been exploited as a fundamental tool for research on aging, revealing crucial lifespan-regulatory pathways. One of the best advantages of *C. elegans* as a model for research on aging is that the *C. elegans* lifespan is only a few weeks. In addition, *C. elegans* undergoes clear age-dependent physiologic and behavioral changes and possesses many lifespan-regulatory pathways that are conserved across phyla. In fact, many evolutionarily conserved genes and pathways that affect organismal longevity were first identified in *C. elegans.*

The first lifespan-regulatory pathway identified in *C. elegans* was the insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway. Subsequent research led to the identification of target of rapamycin (TOR) signaling, dietary restriction (DR), steroid signaling, autophagy, reduced mitochondrial respiration, the hypoxia inducible factor 1 (HIF-1) pathway, and the sensory and reproductive systems as major lifespan-regulatory pathways in *C. elegans*. The identification of genes acting in those pathways and systems shed light on ensuing research in more complex organisms by revealing that many of the pathways are indeed evolutionarily conserved. In this chapter, we will review the roles and mechanisms by which key genes in lifespan-regulatory pathways modulate *C. elegans* lifespan. We include a table with an extensive list of *C. elegans* longevity-influencing genes, many of which are not described in the text due to space limits (Table 8.1). Furthermore, we speculate regarding the physiologic natures of the lifespan-regulatory pathways and possible reasons why these pathways modulate aging in *C. elegans*.

Table 8.1 *C. elegans* genes that affect lifespan via acting in representative longevity pathways

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
aak-2	*PRKAA2*	Catalytic alpha subunit of AMP-activated protein kinase (AMPK)	TOR, DR, Mit	Increase^{OE}	S.L.^{m} of *rsks-1(−), DR, isp-1(−), clk-1(−), sir-2.1^{OE}*, ROS	Apfeld et al. (2004), Curtis et al. (2006), Greer et al. (2007), Selman et al. (2009), Seo et al. (2013), Hwang et al. (2014)
					Decrease^{m}	
aakb-2	*PRKAB2*	Regulatory beta subunit of AMPK	Mit	ND	S.L.^{m} of ROS	Hwang et al. (2014)
					Decrease^{m}	
aakg-4	*PRKAG1*	Regulatory gamma subunit of AMPK	IIS	ND	S.L.$^{m, i}$ of *daf-2(−)*	Tullet et al. (2014)
aap-1	*PIK3R3*	Phosphoinositide 3-kinase (PI3K) adaptor subunit	IIS	ND	Increase^{m} (25.5 °C)	Wolkow et al. (2002)
age-1	*RIK3CA*	Phosphoinositide 3-kinase (PI3K)	IIS	ND	Increase$^{m, i}$	Friedman and Johnson (1988)
aha-1	*HIF*β	Aryl hydrocarbon receptor nuclear translocator	Mit, HIF	ND	S.L.^{i} of *isp-1(−), clk-1(−), tpk-1(−)*	Lee et al. (2010), Khan et al. (2013)
akt-1	*AKT1*	Serine/threonine kinase Akt/PKB	IIS	ND	Increase$^{m, i}$	Hertweck et al. (2004), Hamilton et al. (2005), Tullet et al. (2008), Zhang et al. (2008), Shen et al. (2012)
akt-2	*AKT3*	Serine/threonine kinase Akt/PKB	IIS	ND	Increase^{i}	Hertweck et al. (2004), Tullet et al. (2008)
aqp-1/dod-4	*AQP10*	Aquaporin	IIS, Mit	ND	S.L.^{i} of *clk-1(−)*	Cristina et al. (2009), Lee et al. (2009)
					Decrease^{m}	
atg-18	*WIPI1/2*	WD40 repeat-containing protein	IIS, TOR, Atg, Mit, Rpd	ND	S.L.^{m} of *daf-2(−), let-363 (RNAi), clk-1(−), atp-3(RNAi)*	Toth et al. (2008), Lapierre et al. (2011), Lapierre et al. (2013a)
					S.L.^{i} of g. c.(−), *rsks-1(−)*	
					Decrease^{m}	

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Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
atg-4.1	*ATG4A*	Cysteine protease ATG4A	DR, Atg	ND	S.L.[i] of *mir-34(−)*	Yang et al. (2013)
atg-7	*ATG7*	E1 ubiquitin-activating-like enzyme	DR, Atg	ND	S.L.[i] of DR	Jia and Levine (2007), Hashimoto et al. (2009)
					Increase[i]	
atg-9	*ATG9A*	Autophagy-related protein 9A	DR, Atg	ND	S.L.[i] of *mir-34(−), daf-2(−)*	Toth et al. (2008), Yang et al. (2013)
					Decrease[i]	
atp-2	*ATP5B*	F1 portion of ATP synthase	Mit	ND	Increase[m]	Tsang et al. (2001)
atp-3	*ATP5O*	ATP synthase subunit	Mit	ND	Increase[i]	Dillin et al. (2002b)
bar-1	*JUP*	Beta-catenin	IIS	ND	Decrease[m]	Essers et al. (2005)
bec-1	*BECN1*	Class III phosphatidylinositol 3-kinase complex	IIS, TOR, DR, Atg, Rpd	ND	S.L. [m, i] of *daf-2(−)*, DR, *daf-15/+*, g.c.(−), *mir-34(−), let-363(RNAi), atp-3(RNAi), frh-1(RNAi)*	Melendez et al. (2003), Jia and Levine (2007), Hansen et al. (2008), Toth et al. (2008), Hashimoto et al. (2009), Lapierre et al. (2011), Schiavi et al. (2013), Yang et al. (2013)
					Decrease[m, i]	
					Increase[i]	
cbp-1	*CREBBP*	CREB binding protein	IIS, DR	ND	S.L.[i] of DR, *daf-2(−), mir-80 (−)*	Zhang et al. (2009a), Vora et al. (2013)
					Decrease[i]	
cco-1	*COX5B*	Cytochrome C oxidase	Mit	ND	Increase[i]	Dillin et al. (2002b)
ced-3	*CASP2*	Caspase, a cysteine-aspartate protease, CASP9-like	Mit	ND	S.L.[m] *isp-1(−), nuo-6(−),* ROS	Yee et al. (2014)
ced-4	*APAF1*	Apoptotic peptidase activating factor 1-like	Mit	ND	S.L.[m] *isp-1(−), nuo-6(−),* ROS	Yee et al. (2014)
ced-9	*BCL2L2*	Bcl-2-like	Mit	ND	S.L.[m] *isp-1(−), nuo-6(−),* ROS	Yee et al. (2014)
ced-13	–	BH3 domain	Mit	ND	S.L.[m] of *isp-1(−), nuo-6(−)*	Yee et al. (2014)
ceh-23	*EMX2*	Transcription factor	Mit	Increase[OE]	S.L.[m] of *isp-1(−), clk-1(−)*	Walter et al. (2011)

cep-1	*p53*	p53-like transcription factor	Mit	ND	S.L.[m] of *isp-1(−)*, *nuo-6(−)*	Torgovnick et al. (2010), Baruah et al. (2014)
che-2	*IFT80*	Intraflagellar transport	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
che-3	*DNAH9*	Dynein heavy chain (DHC)	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
che-11	*IFT140*	Intraflagellar transport	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
che-13	*IFT57*	Intraflagellar transport	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
clk-1	*COQ7/ CAT5*	Demethoxyubiquinone (DMQ) hydroxylase	Mit	ND	Increase[m]	Wong et al. (1995), Braeckman et al. (1999)
col-10[#]	*COL3A1*	Collagen	IIS, TOR, DR, Rpd	Increase[OE]	S.L.[i] of *daf-2(−)*(15 °C), TOR, DR, g.c.(−)	Ewald et al. (2014)
col-13[#]	*COL3A1*	Collagen	IIS, TOR, DR, Rpd	Increase[OE]	S.L.[i] of *daf-2(−)*(15 °C), TOR, DR, g.c.(−) Decrease[i] in *daf-2(−)* (20 °C)	Ewald et al. (2014)
col-120[#]	*COL10A1*	Collagen	IIS, TOR, DR, Rpd	Increase[OE]	S.L.[i] of *daf-2(−)*(15 °C), TOR, DR, g.c.(−)	Ewald et al. (2014)
cst-1	*Serine/ threonine protein kinase 3*	Serine/threonine protein kinase	IIS	Increase[OE]	S.L.[i] of *daf-2(−)*	Lehtinen et al. (2006)
cul-1	*CUL1*	Scaffolding protein	IIS	ND	S.L.[i] of *daf-2(−)* Decrease[i]	Ghazi et al. (2007)
cup-4	*CHRNB1*	non-alpha ligand-gated ion channel	DR	Decrease[OE]	S.L.[m, i] of DR Decrease[m, i]	Park et al. (2010)
cyc-1	*CYC1*	Cytochrome C reductase	Mit	ND	Increase[i]	Dillin et al. (2002b)
daf-2	*INSR/IGF-1R*	Insulin receptor	IIS	ND	Increase[m, i]	Kenyon et al. (1993), Dillin et al. (2002a)
daf-6	*PTCHD3*	Patched domain- containing protein	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
daf-7[#]	*GDF11*	Transforming growth factor beta superfamily	IIS	ND	Increase[m]	Shaw et al. (2007)

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Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
daf-9[*#]	*CYP2U1*	Cytochrome P450	IIS, DR, SN, Rpd,	No change[OE]	S.L.[m] of *daf-2(−)*, DR, g.c.(−)	Gerisch et al. (2001), Jia et al. (2002), Gerisch et al. (2007), Lee and Kenyon (2009), Thondamal et al. (2014)
					Decrease[m]	
					Increase[m]	
daf-10	*IFT122*	Intraflagellar transport	SN	ND	Increase[m]	Apfeld and Kenyon (1999)
daf-11	–	Guanylyl cylase	SN	ND	Increase[m]	Hahm et al. (2009)
daf-12[*]	*NR1H3*	Nuclear receptor subfamily 1	IIS, SN, Rpd	Increase[gf] (20 °C)	S.S.[m] of thermosensory mutants (25 °C)	Larsen et al. (1995), Gems et al. (1998), Hsin and Kenyon (1999), Fisher and Lithgow (2006), Berman and Kenyon (2006), Lee and Kenyon (2009)
					S.L.[m, i] of g.c.(−), weak *daf-2 (−)* alleles	
					Decrease[m]	
daf-15	*RAPTOR*	Regulatory associated protein of mTOR	IIS, TOR, DR	ND	Increase[m/+, i] (22.5 °C)	Jia et al. (2004), Ching et al. (2010), Seo et al. (2013)
daf-16	*FOXO*	Transcription factor	IIS, TOR, DR, SN, Rpd,	Increase[OE]	S.L.[m] of *daf-2(−)*, *ifg-1 (RNAi)*, *ragc-1(RNAi)*, *rsks-1 (−), daf-2(−); rsks-1(−)*, *mir-80(−)*, sensory mutants, g.c. (−), DR, *daf-15(+/−)*	Kenyon et al. (1993), Apfeld and Kenyon (1999), Hsin and Kenyon (1999), Lin et al. (2001), Boehm and Slack (2005), Berman and Kenyon (2006), Greer et al. (2007) Hansen et al. (2007), Steinkraus et al. (2008), Zhang et al. (2009a), de Lencastre et al. (2010), Yang et al. (2011), Robida-Stubbs et al. (2012), Chen et al. (2013b), Seo et al. (2013), Vora et al. (2013), Riera et al. (2014)
					S.L.[i] of *daf-2(−)*, *ife-2(−)*, *lin-14(−)*, *mir-239(−)*, g.c.(−)	
					Decrease[m, i]	

daf-18	*PTEN*	Lipid phosphatase	IIS	Increase^{OE}	S.L.^{m}of *daf-2(−)* Decrease^{m}	Dorman et al. (1995), Larsen et al. (1995), Mihaylova et al. (1999), Masse et al. (2005), Brisbin et al. (2009)
daf-19	*RFX2*	Transcription factor	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
daf-28	insulin	Beta-type insulin	IIS	ND	Increase$^{i,\ dn}$	Malone et al. (1996), Okuyama et al. (2010)
daf-36	*RFESDP1*	Rieske oxygenase	Rpd	ND	S.L.^{m} of g.c.(−) Decrease^{m}	Rottiers et al. (2006), Gerisch et al. (2007)
ddl-1	*CCD53*	Coiled-coil protein	IIS	ND	Increase^{i}	Hansen et al. (2005), Chiang et al. (2012)
ddl-2	*WASH2P*	Proline-rich domains	IIS	ND	Increase^{i}	Hansen et al. (2005), Chiang et al. (2012)
dhs-16	*SDR9C7*	Short chain dehydrogenase/ reductase family	Rpd	ND	S.L.^{m} of g.c.(−)	Wollam et al. (2012)
dox-1	*KIN17*	DNA and RNA binding protein	IIS	ND	Decrease^{i} S.L.^{i} of *daf-2(−)*	Henis-Korenblit et al. (2010)
drp-1	*DRP1*	Dynamin-related protein	IIS	ND	Increase^{m,i} in *daf-2(−)*	Yang et al. (2011)
drr-2	*eIF4H*	Eukaryotic translation initiation factor	TOR, DR	S.L.^{OE} of *let-363(RNAi); daf-15(RNAi)*, DR No change^{OE}	Increase^{i}	Hansen et al. (2005), Ching et al. (2010)
dve-1	*SATB1*	SATB homeobox 1 transcription factor	Mit, DR	ND	S.L.^{i} of DR, *isp-1(−)* Decrease^{i}	Zhang et al. (2009a), Durieux et al. (2011)
eak-3	*RNF11*	RING finger protein 11	IIS	ND	Increase ^{m} in *daf-2(−)*	Zhang et al. (2008)
eak-7	*TLDC1*	TBC/LysM-associated domain containing 1	IIS	ND	Increase$^{m,\ i}$	Samuelson et al. (2007), Alam et al. (2010)
eat-2	*CHRNA7*	Ligand-gated ion channel subunit	DR	ND	Increase^{m}	Lakowski and Hekimi (1998)
egl-9	*EGLN1*	Proline hydroxylase	DR, HIF	ND	S.L.^{m} of DR Increase$^{m,\ i}$	Chen et al. (2009), Mehta et al. (2009), Lee et al. (2010)
egl-27	*MTA1*	Metastasis-associated protein	IIS	Increase^{OE}	S.L.^{i} of *daf-2(−)* Decrease^{m}	Xu and Kim (2012)

(continued)

Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
elt-3	*GATA3*	GATA transcription factor 3	IIS	ND	S.L.[m, i] of *daf-2(−)*	Budovskaya et al. (2008), Kim et al. (2013) but see Tonsaker et al. (2012)
					Decrease[m, i]	
ets-4	*SPDEF*	ETS class transcription factor (highly similar to SAM pointed domain-containing ETS transcription factor)	IIS	ND	Increase[m, i]	Thyagarajan et al. (2010)
faah-1	*FAAH*	Fatty acid amide hydrolase	DR	Increase[OE]		Lucanic et al. (2011)
fard-1	*FAR1*	Fatty acyl CoA reductase 1	Rpd	ND	S.L.[i] of g.c.(−)	McCormick et al. (2012)
fat-6/fat-7	*SCD*	Stearoyl-CoA desaturase (delta-9 fatty acid desaturase)	Rpd	ND	S.L.[m] of g.c.(−)	Goudeau et al. (2011), Brock et al. (2006)
flcn-1	*FLCN*	Folliculin	HIF	ND	Increase[m, i]	Gharbi et al. (2013) but see Possik et al. (2014)
frh-1	*FXN*	Frataxin	Mit	ND	Increase[i]	Ventura et al. (2005) but see Zarse et al. (2007), Schiavi et al. (2013)
fstr-1/fstr-2/gfi-1	*Mucin-5 AC (Fragment)*	–	Mit	ND	S.L.[i] of *clk-1(−)*	Cristina et al. (2009)
ftn-1/ftn-2	*FTH1*	Ferritin	Mit	ND	S.L.[i] of *isp-1(−), nuo-6(−)*	Baruah et al. (2014), Hwang et al. (2014)
					S.S.[i] of *isp-1(−); hif-1(−)*	
ftt-2	*YWHAZ*	Tyrosine 3-monooxygenase/ tryptophan 5-monooxygenase activation protein	IIS, Rpd	Increase[OE]	S.L.[i] of *daf-2(−)*,g.c.(−)	Berdichevsky et al. (2006), Wang et al. (2006), Araiz (2008), McCormick et al. (2012), Li et al. (2007a)
					Decrease[i]	
gcn-2	*EIF2AK4*	Eukaryotic translation initiation factor 2 alpha kinase 4	Mit	ND	S.L.[i] of *clk-1(−)*	Baker et al. (2012)
glp-1	*NOTCH1*	N-glycosylated transmembrane protein	Rpd	Decrease[gf]	Increase[m, i]	Arantes-Oliveira et al. (2002), Curran and Ruvkun (2007)

glp-4	–	–	Rpd	ND	Increase[m]	Arantes-Oliveira et al. (2002)
gpa-1	*GNAO1*	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	SN	Decrease[OE]	Increase[m]	Lans and Jansen (2007)
gpa-2	*GNAO1*	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	SN	Increase[OE]	Decrease[m]	Lans and Jansen (2007)
gpa-3	*GNAO1*	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	SN	Increase[gf] No change[gf]	Decrease[m]	Lans and Jansen (2007), Hahm et al. (2009)
gpa-5	–	G protein	SN	No change[OE]	Increase[m]	Lans and Jansen (2007)
gpa-9	*GNAI2*	Guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 2	SN	Decrease[OE]	Increase[m]	Lans and Jansen (2007)
gpa-10	*GNAT3*	Guanine nucleotide binding protein, alpha transducing 3	SN	ND	Decrease[m]	Lans and Jansen (2007)
gpa-11	*GNAT3*	Guanine nucleotide binding protein, alpha transducing 3	SN	Increase[OE]		Lans and Jansen (2007)
gpc-1	*GNG7*	Gγ subunit	SN	ND	Increase[m]	Lans and Jansen (2007)
hcf-1	*HCFC1*	Human host cell factor 1	IIS	ND	Increase[m, i]	Li et al. (2008), Rizki et al. (2011)
hif-1[#]	*HIF1A*	Hipoxia-inducible factor 1, transcription factor	DR, Mit, HIF	Increase[OE, gf]	S.L.[m] of *vhl-1(−), egl-9(−)* S.L.[m, i] of *isp-1(−), clk-1(−), daf-15(+/−), rsks-1(−)* S.L.[m] of ROS Increase[m] (25 °C)	Chen et al. (2009), Mehta et al. (2009) Zhang et al. (2009b), Lee et al. (2010), Leiser et al. (2011), Hwang et al. (2014)

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Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
hlh-30	*TFEB*	Basic helix-loop-helix (bHLH) transcription factor	IIS, DR, Atg, Mit, Rpd	Increase^{OE}	S.L.^{m} of *mxl-3(−)*	O'Rourke and Ruvkun (2013). Lapierre et al. (2013a)
					S.L.^{i} of DR, *daf-2(−)*, *clk-1(−)*, *rsks-1(−)*, g.c.(−)	
					Decrease^{m}	
hsf-1	*HSF1*	Heat-shock transcription factor	IIS, TOR, DR	Increase^{OE}	S.L.^{m} of *daf-2(−)*, *rsks-1(−)*, *daf-2(−); rsks-1(−)*, *rps-6 (RNAi)*, *rps-15(RNAi)*, *mir-80 (−)*, *ddl-1(RNAi)*, *ddl-2 (RNAi)*, DR	Hsu et al. (2003), Morley and Morimoto (2004), Steinkraus et al. (2008), Lee and Kenyon (2009), Zhang et al. (2009a), Chiang et al. (2012), Seo et al. (2013), Vora et al. (2013)
					S.L.^{i} of *daf-2(−)*, *age-1(−)*	
					Decrease$^{m, i}$	
hsp-16/ 16.1/16.2/ 16.11/ 16.49	*HSPB5*	Heat shock protein	IIS, TOR	ND	Decrease^{i}	Hsu et al. (2003), Morley and Morimoto, (2004), Seo et al. (2013)
					S.L.^{i} of *daf-2(−)*, *age-1(−)*, *rsks-1(−)*, *hsf-1*^{OE}	
ife-2	*eIF4E*	Translation initiation factor 4E (eIF4E) family	IIS, TOR	ND	Increase$^{m, i}$	Hansen et al. (2007), Syntichaki et al. (2007)
					S.L.^{i} of *daf-2(−)*, *age-1(−)*	
ifg-1	*eIF4G*	Translation initiation factor 4G (eIF4G) family	IIS, TOR	ND	Increase^{i}	Curran and Ruvkun (2007), Hansen et al. (2007), Pan et al. (2007)
					S.L.^{i} of *daf-2(−)*	
iftb-1	*eIF2S2*	eIF2beta translation initiation factor	IIS	ND	S.L.^{i} of *daf-2(−)*	Hansen et al. (2007)
					Increase^{i}	
ins-1	–	Insulin/IGF-like peptides	IIS	Increase^{OE} (26 °C)	Increase^{m}	Pierce et al. (2001)
ins-7	–	Insulin/IGF-like peptides	IIS	Decrease^{OE}	Increase$^{m, i}$	Murphy et al. (2003), Murphy et al. (2007), Matsunaga et al. (2012)
ins-18	–	Insulin/IGF-like peptides	IIS	Increase^{OE} (25 °C)	S.L.^{m} of *daf-2(−)*, *ins-7(−)*	Matsunaga et al. (2012)

ire-1	*ERN1*	Serine/threonine-protein kinase/endoribonuclease IRE1	IIS	ND	Decrease$^{m, i}$	Henis-Korenblit et al. (2010)
					S.L.$^{m, i}$ of *daf-2(−)*	
isw-1	*SMARCA1*	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1	IIS	ND	S.L.^{i} of *daf-2(−)*	Curran et al. (2009)
isp-1	*UQCRFS1*	Rieske iron sulphur protein	Mit	ND	Increase$^{m, i}$	Feng et al. (2001), Rea et al. (2007)
jnk-1	*MAPK10*	Serine/threonine kinase	IIS	Increase^{OE}	Decrease^{m}	Oh et al. (2005)
kin-29	*SIK3*	Serine/threonine-protein kinase SIK3	SN	ND	Increase^{m}	Lanjuin and Sengupta (2002)
klf-1	*KLF4*	Krueppel-like factor 4 transcription factor	DR	Increase^{OE}	S.L.^{i} of DR	Carrano et al. (2014)
kri-1	*KRIT1*	Krev interaction trapped/cerebral cavernous malformation 1	Rpd	Increase^{OE}	S.L.$^{m, i}$ of g.c.(−)	Berman and Kenyon (2006)
let-363	*MTOR*	Mechanistic target of rapamycin, serine/threonine kinase	TOR, DR	ND	Increase$^{m, i}$	Vellai et al. (2003), Hansen et al. (2007)
let-60	*KRAS*	GTPase KRas	IIS	Decrease^{gf}	S.L.^{m} of *daf-2(−)*	Nanji et al. (2005)
					Decrease^{m}	
lgg-1	*GABARAP*	LC3, GABARAP and GATE-16 family Gamma-aminobutyric acid receptor-associated protein	Atg, Rpd	ND	S.L.^{i} of *daf-2(−)*, g.c.(−)	Toth et al. (2008), Lapierre et al. (2011)
					Decrease^{i}	
lin-4	–	MicroRNA	IIS	Increase^{OE}	S.L.^{m} of *daf-2(−)*	Boehm and Slack (2005)
					Decrease^{m}	
lin-14	–	ND	IIS, Rpd	Decrease^{gf}	S.S.$^{m, i}$ of *lin-4(−)*	Boehm and Slack (2005), Shen et al. (2012)
					S.S.^{i} of *mir-84(−); mir-241(−)*; g.c.(−)	
					Increase$^{m, i}$	

(continued)

Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
lipl-4	*LIPM*	Lipase member M	Atg, Rpd	Increase^{OE}	S.L.^{i} of g.c.(−)	Wang et al. (2008), Lapierre et al. (2011)
lips-17	–	Triacylglycerol lipase	Rpd	ND	S.L.^{i} of g.c.(−)	McCormick et al. (2012)
mct-1/2	*MCT9*	Monocarboxylate transporter	SN	Increase^{OE}	S.L.^{i} of *daf-10(−)*	Gaglia et al. (2012)
mdl-1	*MXI1*	Basic helix-loop-helix (bHLH) protein	IIS		Increase^{m}	Johnson et al. (2014)
mec-8	*RBPMS2*	RNA binding	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
mekk-3	–	Kinase	DR	ND	Increase^{i}	Chamoli et al. (2014)
mes-1	*TYK2*	Receptor tyrosine kinase-like protein	IIS, Rpd	ND	Increase^{m}	Arantes-Oliveira et al. (2002)
mes-4	*WHSC1*	SET domain-containing protein that also contains three plant homeodomain (PHD) fingers	IIS	ND	S.L.^{i} of *daf-2(−)* Increase^{i}	Curran et al. (2009)
mir-34	–	MicroRNA	DR, Atg	ND	S.L.^{m} of DR Increase^{m}	Yang et al. (2013)
mir-71	–	MicroRNA	IIS, DR, Rpd	Increase^{OE}	S.L.^{m} of *daf-2(−)*,g.c.(−) Decrease^{m}	de Lencastre et al. (2010), Boulias and Horvitz (2012), Smith-Vikos et al. (2014)
mir-80	–	MicroRNA	IIS, DR	ND	Increase^{m}	Vora et al. (2013)
mir-84/ mir-241	–	MicroRNAs	Rpd	No change^{OE}	S.L.^{m} of g.c.(−)	Shen et al. (2012)
mir-228	–	MicroRNA	DR	Decrease^{OE}	Increase^{m}	Smith-Vikos et al. (2014)
mir-239.1		MicroRNA	IIS	Decrease^{OE}	Increase^{m}	de Lencastre et al. (2010)
mml-1	*MLXIP*	MLX interacting protein	IIS	ND	S.L.^{i} of *daf-2(−)* Decrease^{m}	Johnson et al. (2014)
mrpl-1	*MRPL1*	Mitochondrial ribosomal protein, large	Mit	ND	Increase^{i}	Houtkooper et al. (2013)

mrpl-2	*MRPL2*	Mitochondrial ribosomal protein, large	Mit	ND	Increase[i]	Houtkooper et al. (2013)
mrpl-37	*MRPL37*	Mitochondrial ribosomal protein, large	Mit	ND	Increase[i]	Houtkooper et al. (2013)
mrps-5	*MRPS5*	Mitochondrial ribosomal protein, small	Mit	ND	Increase[i]	Houtkooper et al. (2013)
mxl-1	*MAX*	Basic helix-loop-helix protein	IIS, DR	ND	Increase[m]	Johnson et al. (2014)
mxl-2	*MLX*	Basic helix-loop-helix protein	IIS, DR	ND	S.L.[m] of *daf-2(−)*, DR	Johnson et al. (2014)
		MAX dimerization protein			S.L.[i] of *mdl-1(−)*, *mxl-1(−)*, *daf-2(−)*, DR	
					Decrease[m]	
nhr-8	*NR1H*	Nuclear hormone receptor	DR	ND	S.L.[m] of DR	Thondamal et al. (2014), Magner et al. (2013)
					Decrease[m]	
nhr-49	*NR2A1*	Transcription factor	Mit, Rpd	Increase[OE]	Decrease[m, i]	Van Gilst et al. (2005), Khan et al. (2013), Ratnappan et al. (2014)
					S.L.[m]of g.c.(−)	
					S.L.[i] of *isp-1(−), g.c.(−)*	
nhr-62	*HNF4A*	Transcription factor	DR	ND	S.L.[m, i] of DR	Heestand et al. (2013)
nhr-80	*HNF4A*	Hepatocyte nuclear factor 4-alpha-3	Rpd	No change[OE]	S.L.[m] of g.c.(−)	Brock et al. (2006), Goudeau et al. (2011)
					Slight decrease[m]	
nkcc-1	*NKCC2*	Na-K-Cl cotransporter	Mit	ND	Increase[i]	Houtkooper et al. (2013)
nlp-7	–	Neuropeptide-like protein	DR	Decrease[OE]	S.L.[m,i] of DR	Park et al. (2010)
					Decrease[m,i]	
nmur-1[$]	*NMUR2*	Neuromedin-U receptor 2	SN	ND	Increase[m]	Maier et al. (2010)
nuo-1	*NDUFV1*	NADH ubiquinone oxidoreductase	Mit	ND	Increase[m]	Tsang et al. (2001)
nuo-2	*NDUFS3*	NADH ubiquinone oxidoreductase	Mit	ND	Increase[i]	Dillin et al. (2002b)
nuo-6	*NDUFB4/ B15*	NADH ubiquinone oxidoreductase	Mit	ND	Increase[m]	Yang and Hekimi (2010a)

(continued)

Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
ocr-2	*TRPV6*	Transient receptor potential channel, vanilloid subfamily	SN	ND	Increase^{m}	Lee and Ashrafi (2008), Riera et al. (2014)
odr-2	–	Membrane-associated protein	SN	ND	Increase^{m}	Alcedo and Kenyon (2004)
odr-3	*GNAT3*	G protein	SN	ND	Increase^{m}	Alcedo and Kenyon (2004), Lans and Jansen (2007)
odr-7	*NR2E1*	Olfactory-specific member of the nuclear receptor superfamily	SN	ND	Increase^{m}	Alcedo and Kenyon (2004)
oga-1	*MGEA5*	O-GlcNAc selective N-Acetyl-beta-D-glucosaminidase (O-GlcNAcase)	IIS	ND	Increase^{m}	Rahman et al. (2010)
ogt-1	*OGT*	12 N-terminal tetratri-copeptide (TPR) domains and a C-terminal putative catalytic domain	IIS	ND	S.L.^{m} of *age-1(−)*, *sgk-1(−)*, *daf-2(−)* Decrease^{m}	Rahman et al. (2010)
osm-1	*IFT172*	Intraflagellar transport	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
osm-3	*KIF17*	Kinesin-2 family member	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
osm-5	*IFT88*	Intraflagellar transport	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
osm-6	*IFT52*	Intraflagellar transport	SN	ND	Increase^{m}	Apfeld and Kenyon (1999)
par-4	*LKB1/ STK11*	Serine/threonine protein kinase	Mit	ND	S.L.^{m} of ROS Decrease^{m}	Hwang et al. (2014)
par-5	*YWHAZ*	One of two *C. elegans* 14-3-3 proteins	IIS	Increase^{OE}	Decrease^{i}	Berdichevsky et al. (2006), Wang et al. (2006), Li et al. (2007a)
pdk-1	*PDPK1*	3-phosphoinositide-dependent kinase 1	IIS	Decrease^{gf}	Increase^{m}	Paradis et al. (1999)
pgl-1	*TAF15*	RNA-binding protein	IIS	ND	S.L.^{i} of *daf-2(−)*	Curran et al. (2009)
pgl-2	–	P granule abnormality protein	IIS	ND	S.L.^{i} of *daf-2(−)*	Curran et al. (2009)

pgl-3	–	P granule abnormality protein	IIS	ND	S.L.i of *daf-2(−)*	Curran et al. (2009)
pha-4	*FOXA1*	Forkhead box protein A1 transcription factor	TOR, DR, Rpd	Increase^{OE}	S.L.^{i} of *rsks-1(−)*, DR, *mir-228(−)*, g.c.(−)	Panowski et al. (2007), Sheaffer et al. (2008), Lapierre et al. (2011), Smith-Vikos et al. (2014)
					Decrease^{i}	
phi-62	*RNASEK*	Ribonuclease kappa	DR, Mit, Rpd	ND	S.L.^{i} of *isp-1(−)*, DR, g.c.(−)	McCormick et al. (2012)
					Decrease^{i}	
pie-1	–	Zinc-finger protein	IIS	ND	S.L.^{i} of *daf-2(−)*	Curran et al. (2009)
pnc-1	–	pyrazinamidase/ nicotinamidase	DR	ND	S.L.^{m} by DR	van der Horst et al. (2007), Moroz et al. (2014)
					Decrease^{i}	
pptr-1	*PPP2R5E*	PP2A holoenzyme regulatory subunit	IIS	Increase^{OE}	S.L.^{i} of *daf-2(−)*	Padmanabhan et al. (2009)
pqm-1	–	C2H2-type zinc finger and leucine zipper-containing protein	IIS	Decrease^{OE}	S.L.$^{m, i}$ of *daf-2(−)*	Tepper et al. (2013)
prmt-1	*PRMT1*	Type I protein arginine methyltransferase	IIS	No change^{OE}	S.L.^{m} of *daf-2(−)*	Takahashi et al. (2011)
					Decrease^{m}	
rab-10	*RAB10*	Rab-like GTPase	DR	ND	Increase^{i}	Hansen et al. (2005)
raga-1	*RagA*	Ras-related GTP binding protein A	IIS, TOR, DR	Decrease^{gf}, Increase^{dn}	Increase$^{m, i}$	Schreiber et al. (2010), Robida-Stubbs et al. (2012)
ragc-1	*RagC*	Ras-related GTP binding protein C	IIS, TOR	ND	Increase^{i}	Robida-Stubbs et al. (2012), Seo et al. (2013)
rheb-1	*Rheb*	Rheb GTPase	TOR, DR	ND	Increase^{i}	Honjoh et al. (2009)
rict-1$^{\$}$	*RICTOR*	Rapamycin insensitive companion of mTOR	TOR	ND	Decrease^{m}	Soukas et al. (2009)
rle-1	*RC3H1*	E3 ubiquitin ligase	IIS	ND	Increase^{m}	Li et al. (2007b)
rpl-4	*RPL4*	Ribosomal subunit	TOR	ND	Increase^{i}	Hansen et al. (2007)
rpl-6	*RPL6*	Ribosomal subunit	TOR	ND	Increase^{i}	Hansen et al. (2007)
rpl-9	*RPL9*	Ribosomal subunit	TOR	ND	Increase^{i}	Hansen et al. (2007)
rpl-19	*RPL19*	Ribosomal subunit	TOR	ND	Increase^{i}	Hansen et al. (2007)
rpl-30	*RPL30*	Ribosomal subunit	TOR	ND	Increase^{i}	Hansen et al. (2007)

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Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
rps-3	*RPS3*	Ribosomal subunit	TOR	ND	Increase[i]	Curran and Ruvkun (2007)
rps-5	*RPS5*	Ribosomal subunit	TOR	ND	Increase[i]	Kim and Sun (2007)
rps-6	*RPS6*	Ribosomal subunit	TOR	ND	Increase[i]	Hansen et al. (2007), Seo et al. (2013)
rps-8	*RPS8*	Ribosomal subunit	TOR	ND	Increase[i]	Curran and Ruvkun (2007)
rps-10	*RPS10*	Ribosomal subunit	TOR	ND	Increase[i]	Hansen et al. (2007)
rps-11	*RPS11*	Ribosomal subunit	TOR	ND	Increase[i]	Curran and Ruvkun (2007), Hansen et al. (2007)
rps-15	*RPS15*	Ribosomal subunit	TOR	ND	Increase[i]	Hansen et al. (2007), Seo et al. (2013)
rps-22	*RPS22*	Ribosomal subunit	TOR	ND	Increase[i]	Hansen et al. (2007)
rps-23	*RPS23*	Ribosomal subunit	TOR	ND	Increase[i]	Kim and Sun (2007)
rps-26	*RPS26*	Ribosomal subunit	TOR	ND	Increase[i]	Hansen et al. (2007)
rsks-1	*RPS6KB*	Ribosomal subunit 6 kinase	TOR	ND	Increase[m, i]	Hansen et al. (2007), Pan et al. (2007), Seo et al. (2013)
sams-1	*MAT1A*	S-adenosyl methionine synthetase	DR	ND	Increase[i]	Hansen et al. (2005)
sea-2	*EP400*	Functions to interpret the X: A chromosomal ratio	IIS	ND	Increase[m, i] Increase[m] in *daf-2(−)*	Huang et al. (2011)
sem-5	*GRB2*	Src homology (SH) domain 2 and 3-containing protein	IIS	ND	S.L.[m] of *daf-2(−)*	Nanji et al. (2005)
ser-3	*ADRA1A*	Octopamine receptor	SN	ND	Increase[m]	Petrascheck et al. (2007)
ser-4	*HTR1B*	Serotonin receptor	SN	ND	Increase[m]	Petrascheck et al. (2007)

sgk-1	*SGK1*	Serine/threonine protein kinase	IIS, TOR	Increase[gf], Decrease[OE], Increase[OE] (intestine)	S.L.[m] of *akt-1(−)*, *trpa-1*[OE] Decrease[m] Increase[i]	Hertweck et al. (2004), Tullet et al. (2008), Soukas et al. (2009), Alam et al. (2010), Rahman et al. (2010), Chen et al. (2013a), Xiao et al. (2013)
shc-1	*SHC1*	Src Homology domain C-terminal adaptor homolog	IIS	No change[OE]	S.L.[m] of *daf-2(−)* Decrease[m]	Neumann-Haefelin et al. (2008)
sir-2.1	*SIRT1*	NAD-dependent protein deacetylase	IIS, DR	Increase[OE]	S.L.[m] of DR Decrease[m, i]	Tissenbaum and Guarente (2001), Wang and Tissenbaum (2006), Berdichevsky et al. (2006), Rizki et al. (2011), Mouchiroud et al. (2013), Schmeisser et al. (2013) but see Burnett et al. (2011), Viswanathan and Guarente (2011)
				No change[OE]	Increase[i]	
skn-1	*NFE2L2*	bZip transcription factor	IIS, TOR, DR	Increase[OE]	S.L.[m] of *daf-2(−)*, DR, *ife-2 (RNAi), ragc-1(RNAi)* S.L.[i] of *mir-228(−)* Decrease[m, i]	Bishop and Guarente (2007), Tullet et al. (2008), Wang et al. (2010), Okuyama et al. (2010), Robida-Stubbs et al. (2012), Smith-Vikos et al. (2014)
skr-1/2	*SKP1*	SKP1-related (ubiquitin ligase complex component)	IIS	ND	S.L.[i] of *daf-2(−)* Decrease[i]	Ghazi et al. (2007)
smk-1	*SMEK1*	Mammalian and Dictyostelium discoideum SMEK (suppressor of MEK null)	IIS, DR, Rpd	ND	Decrease[i] S.L.[i] of *daf-2(−)*, DR, g.c.(−)	Wolff et al. (2006), Panowski et al. (2007)

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Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
sod-2	*SOD2*	Mitochondrial superoxide dismutase	Mit	Increase^{OE}	S.L.^{m} of *isp-1(−)*	Yang et al. (2007), Van Raamsdonk and Hekimi (2009), Cabreiro et al. (2011)
					Increase^{m} of *clk-1(−)*, DR, g.c.(−)	
sod-3	*SOD3*	Mitochondrial superoxide dismutase	Mit	ND	S.L.^{m} of ROS	Yee et al. (2014)
sos-1	*SOS1/2*	Ras-activating guanine nucleotide exchange factor (GEF)	IIS	ND	S.L.^{m} of *daf-2(−)*	Nanji et al. (2005)
str-2	–	G protein-coupled receptor	SN	ND	Increase^{i}	Alcedo and Kenyon (2004)
taf-4	*TAF4B*	Component of transcription factor TFIID complex	Mit	ND	S.L.^{i} of *isp-1(−)*, *clk-1(−)*, *tpk-1(−)*	Khan et al. (2013)
tax-2$^{\#}$	*CNGB3*	Cyclic nucleotide-gated channel β-subunit	SN	ND	Increase^{m} (15 °C, 20 °C)	Apfeld and Kenyon (1999), Lee and Kenyon (2009)
					Decrease^{m} (25 °C)	
tax-4$^{\#}$	*CNGA1*	Cyclic nucleotide-gated channel α-subunit	SN	ND	Increase^{m} (15 °C, 20 °C)	Apfeld and Kenyon (1999), Lee and Kenyon (2009)
					Decrease^{m} (25 °C)	
tcer-1	*TCERG1*	Transcription elongation regulator	Rpd	Increase^{OE}	S.L.$^{m, i}$ of g.c.(−)	Ghazi et al. (2009)
tpk-1	*TPK1*	Thiamine pyrophosphokinase	Mit	ND	Increase^{m}	de Jong et al. (2004)
trpa-1$^{\#}$	*TRPA1*	cold-sensitive transient receptor potential ion channel subfamily A	SN, IIS	Increase^{OE} (20 °C and 15 °C)	Decrease^{m} (20 °C and 15 °C)	Xiao et al. (2013)
				No change^{OE} (25 °C)		

tts-1	–	transcribed telomeric sequence 1/long noncoding RNA (lncRNA)	IIS, Mit	ND	S.L.[i] of *daf-2(−)*, and *clk-1(−)*	Essers et al. (2015)
ttx-1[#]	*OTX1*	Homeodomain transcription factor	SN	ND	Decrease[m] (25 °C)	Lee and Kenyon (2009)
tub-1	*TUB*	Tubby bipartite transcription factor	IIS	ND	Increase[m]	Mukhopadhyay et al. (2005)
ubc-18	*UBE2L3*	E2 ubiquitin-conjugating enzyme	DR	No change[OE]	S.L.[i] of DR	Carrano et al. (2009)
					Decrease[m]	
ubl-5	*UBL5*	Coactivator of DVE-1	Mit	ND	S.L.[i] of *isp-1(−), clk-1(−)*	Durieux et al. (2011), Taylor and Dillin (2013)
					Decrease[i]	
unc-31	*CADPS*	Pleckstrin homology (PH) domain-containing protein	IIS	ND	Increase[m]	Ailion et al. (1999)
unc-51	*ULK2*	Serine/threonine protein kinase orthologous to *S. cerevisiae* Atg1p	TOR, DR, Atg, Mit, Rpd	ND	S.L.[m] of TOR, DR, *atp-3 (RNAi)*	Toth et al. (2008), Lapierre et al. (2011)
					S.L.[i] of g.c.(−)	
					Decrease[m]	
unc-64	*STX1A*	Syntaxin, a plasma membrane receptor	IIS	ND	Increase[m]	Ailion et al. (1999)
utx-1	*KDM6A*	Lysine (K)-specific H3K27 demethylase	IIS	ND	Increase[m/+, i]	Jin et al. (2011), Maures et al. (2011)
vang-1	*VANGL1*	Wnt-directed planar cell polarity (PCP) protein orthologous to *Drosophila* VAN GOGH	IIS	ND	Increase[m, i]	Honnen et al. (2012)
vhl-1	*VHL*	Substrate-recognition subunit of E3 ligase	HIF	ND	Increase[m, i]	Mehta et al. (2009), Muller et al. (2009), Hwang et al. (2014)

(continued)

Table 8.1 (continued)

C. elegans gene	Human ortholog	Gene function/Domains	Pathway(s)	Effects on lifespan		References
				Overexpression/ Gain of function	Loss of function	
vps-34	*PIK3C3*	Phosphoinositide 3-kinase	DR, Atg, Rpd	ND	S.L.^{i} of DR, g.c.(−), *lipl-4*^{OE}, *rab-10(−)*	Hansen et al. (2008), Lapierre et al. (2011)
wwp-1	*WWP1*	HECT E3 ubiquitin ligase	DR	Increase^{OE}	S.L.$^{m, i}$ of DR	Carrano et al. (2009)
xbp-1	*XBP1*	X-box binding protein/bZIP transcription factor	IIS	Increase^{OE} (neurons, intestine)	S.L.^{m} of *daf-2(−)* Decrease^{m,i}	Henis-Korenblit et al. (2010), Taylor and Dillin (2013)
				Decrease^{OE} (muscle)		

These are selected *C. elegans* lifespan-regulatory genes that act in the pathways described in the text

Notes: descriptions regarding loss of function mutations or RNAi of genes, which did not cause lifespan changes, were omitted. Genes that affect lifespan via DAF-16/FOXO were included as IIS genes for simplicity

IIS insulin/IGF-1 signaling, *TOR* target of rapamycin, *DR* dietary restriction, *Atg* autophagy, *Mit* mitochondria, *HIF* hypoxia-inducible factor 1, *ROS* reactive oxygen species, *SN* sensory neurons, *Rpd* reproduction, *g.c.(−)* germ cell ablation. Overexpression (^{OE}), gain of function (^{gf}), dominant negative mutation (^{dn}), loss of function mutations (^{m}), heterozygote loss of function mutations (m/+), and RNAi knockdown (^{i}) of genes, which affect lifespan in *C. elegans*. *C. elegans* lifespan phenotypes that show: *, allele dependency; $^{\#}$, temperature dependency; $^{\$}$, food dependency; decrease or increase, decrease or increase in lifespan; S.L., suppression of longevity; S.S., suppression of short lifespan. ND, not determined

8.2 Longevity-Regulatory Pathways in *C. elegans*

8.2.1 The Insulin/Insulin-Like Growth Factor 1 Signaling Pathway

The insulin/IGF-1 signaling (IIS) pathway is one of the most highly characterized and evolutionarily conserved pathways that regulate aging (Fig. 8.1). In *C. elegans*, IIS is presumably initiated by the modulation of the activity of DAF-2, an insulin/

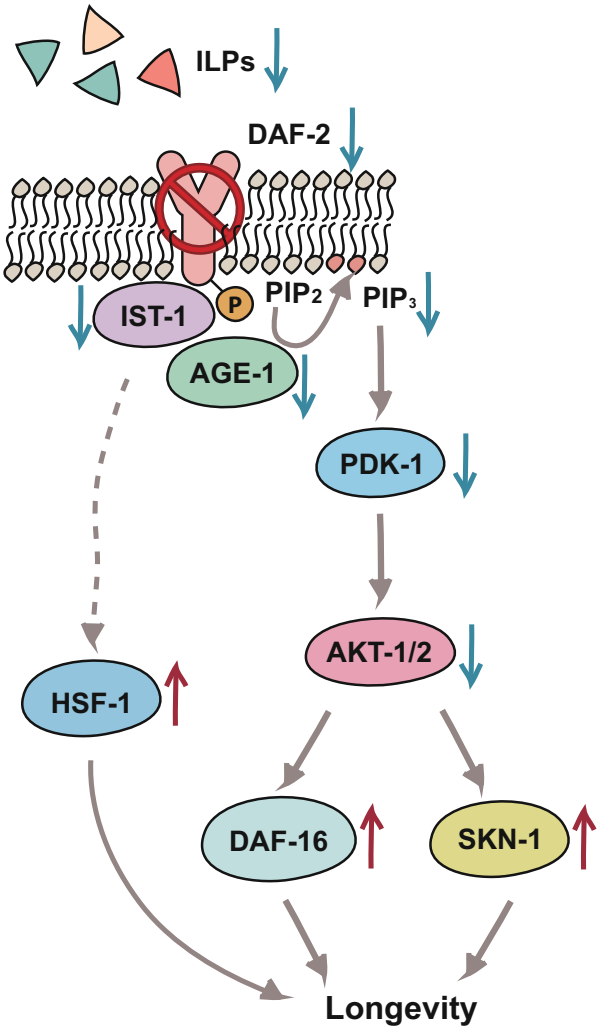

Fig. 8.1 Lifespan regulation by the insulin/IGF-1 signaling pathway in *C. elegans*. Insulin-like peptides (ILPs) bind to insulin/IGF-1 receptor DAF-2 to regulate its phosphorylation. The reduction of DAF-2 activity leads to decreased binding of IST-1, the insulin receptor substrate, resulting in the inactivation of phosphoinositide-3 kinase (AGE-1), which is responsible for the conversion of $PI(4,5)P_2$ to $PI(3,4,5)P_3$. This event decreases the activities of phosphoinositide-dependent kinase 1 (PDK-1) and the AKT-1 and AKT-2 (AKT-1/2) kinases. This reduces the phosphorylation of the DAF-16/FOXO and SKN-1/NRF2 transcription factors, increasing their activities. The inhibition of DAF-2 also increases the activity of heat shock transcription factor 1 (HSF-1). The activation of DAF-16, SKN-1, and HSF-1 leads to longevity by transcriptionally regulating the expression of downstream longevity genes

IGF-1 receptor homolog, upon the binding of insulin-like peptides (ILPs). *C. elegans* expresses 40 ILPs, some of which are predicted to be DAF-2 agonists (e.g., *ins-7*) or antagonists (e.g., *ins-18*) (Kawano et al. 2000; Murphy et al. 2003, 2007; Fernandes de Abreu et al. 2014). The up-regulation of DAF-2 leads to the activation of a phosphoinositide 3-kinase (PI3K) cascade, which in turn regulates several transcription factors that affect lifespan (reviewed in Kaletsky and Murphy 2010; Murphy and Hu 2013).

Many components of IIS regulate lifespan. For example, mutations in *daf-2* can double the lifespan (Kenyon et al. 1993). The importance of DAF-2 as a longevity-regulatory factor is highlighted by the findings that mouse and human DAF-2 homologs are associated with longevity (reviewed in Kenyon 2010). Mutations in *age-1*, which encodes the catalytic subunit of PI3K (Morris et al. 1996), greatly extend lifespan as well (Friedman and Johnson 1988). Other genes in the IIS pathway whose genetic perturbation extends lifespan include *ins-7* and *daf-28*, two ILP genes; *ist-1* (insulin receptor substrate homolog); *pdk-1*, which encodes a phosphoinositide-dependent kinase (PDK); and *akt-1* and *akt-2*, two *C. elegans* Akt/PKB homologs (Murphy et al. 2003; Paradis and Ruvkun 1998; Malone et al. 1996; Paradis et al. 1999; Wolkow et al. 2002). The transcription factors that act downstream of IIS, including DAF-16/FOXO, heat shock factor 1 (HSF-1) and SKN-1/NRF2, are required for longevity in animals with reduced IIS (Kenyon et al. 1993; Lin et al. 1997; Ogg et al. 1997; Hsu et al. 2003; Morley and Morimoto 2004; Tullet et al. 2008). Among those, DAF-16 is the best characterized longevity-promoting transcription factor, and its human homolog FOXO3A is also linked to longevity (reviewed in Kenyon 2010). DAF-16 is inactivated by phosphorylation via AKT-1 and AKT-2, and the dephosphorylation of DAF-16 leads to DAF-16 activation via nuclear localization (Lin et al. 2001; Henderson and Johnson 2001; Lee et al. 2001). The activation of DAF-16 leads to the induction of various genes that are crucial for longevity, including molecular chaperones, antioxidants, anti-microbials, and stress resistance genes (reviewed in Kaletsky and Murphy 2010; Murphy and Hu 2013). Many other longevity-regulatory genes involved in IIS have been identified using genetic, genomic, and proteomic approaches (Table 8.1). It will be important to characterize the relationships among those many factors to ascertain their impact on lifespan regulation.

What is the physiologic interpretation of the effects of IIS on longevity? IIS influences not only longevity but also other physiologic processes including larval development, fat metabolism, immunity, and stress resistance (reviewed in Kaletsky and Murphy 2010; Murphy and Hu 2013). Increased resistance to various stresses, including heat (Lithgow et al. 1995), osmotic stress (Lamitina and Strange 2005), reactive oxygen species (ROS) (Honda and Honda 1999), hypoxia (Scott et al. 2002) and endoplasmic reticulum (ER) stress (Henis-Korenblit et al. 2010), and proteotoxicity (Morley et al. 2002; Hsu et al. 2003) will confer survival benefits to *C. elegans* in general. At the cellular level, the stress resistance phenotypes might contribute to longevity by promoting cellular maintenance capabilities. In addition, animals with reduced IIS have higher chances to survive infection by various pathogens because of enhanced innate immunity (Garsin et al. 2003). This appears

to lengthen lifespan in *C. elegans*, because the main cause of death in aged *C. elegans* in laboratory is infection by *E. coli*, the worm's bacterial food (Garigan et al. 2002). Moreover, somatic cells in *C. elegans* with reduced IIS have the characteristics of germline stem cells, which are robustly protected from various stresses (Curran et al. 2009). Overall, *C. elegans* appears to employ endocrine IIS to enhance cellular protection and maintenance in the face of harsh environmental conditions, which may lead to longevity.

8.2.2 *Lifespan-Regulating Genes in the Target of Rapamycin (TOR) Signaling Pathway*

The TOR pathway is another evolutionarily well-conserved signaling pathway that influences aging (Fig. 8.2). TOR is a serine/threonine kinase that plays various physiologic roles, including involvement in cellular growth, metabolism, protein synthesis and autophagy, and aging, in response to changes in nutrient status (Stanfel et al. 2009; Kapahi et al. 2010; Evans et al. 2011; Laplante and Sabatini 2012; Johnson et al. 2013). TOR interacts with other proteins such as the regulatory-associated protein raptor and the rapamycin-insensitive companion rictor. Those interactions determine the formation of TOR complex 1 (TORC1) and TOR complex 2 (TORC2), respectively. Although both complexes are linked to longevity, the signaling pathway of TORC1 is characterized in more detail than that

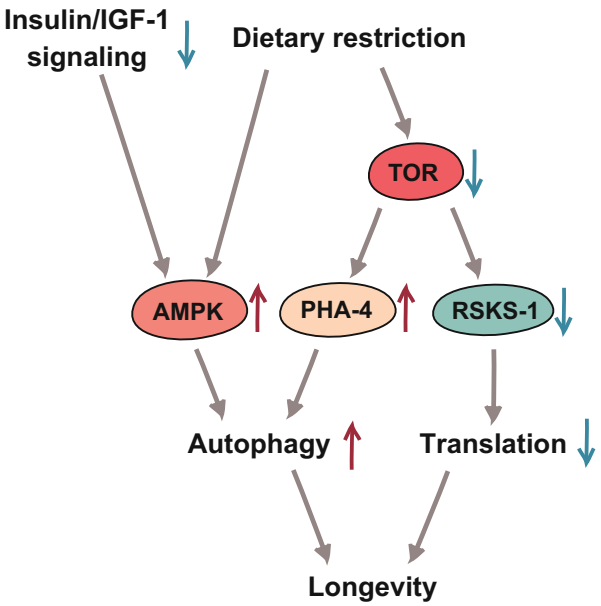

Fig. 8.2 Dietary restriction increases lifespan through AMPK, TOR signaling, and autophagy. Dietary restriction extends lifespan through energy-sensing pathways in general. Dietary restriction increases the activity of AMP-activated protein kinase (AMPK) while down-regulating target of rapamycin (TOR) kinase. Activated AMPK extends lifespan partly by increasing autophagy. Reduced TOR signaling leads to the activation of autophagy via PHA-4/FOXA and the reduction of translation via the down-regulation of ribosomal S6 kinase 1 (RSKS-1)

of TORC2. TORC1 exerts its effects by regulating downstream targets, including ribosomal protein S6 kinase, which promotes protein synthesis via the phosphorylation of ribosomal protein subunit 6.

The inhibition of various TOR pathway genes extends the lifespan of *C. elegans*. The RNAi knockdown or mutation of *let-363*/TOR, *daf-15*/RAPTOR, *rsks-1* (ribosomal protein S6 kinase), ribosomal subunits, or translational initiation factors increases the lifespan of *C. elegans* (Vellai et al. 2003; Jia et al. 2004; Ching et al. 2010; Chen et al. 2013b; Seo et al. 2013; Hansen et al. 2007; Pan et al. 2007; Syntichaki et al. 2007; Curran and Ruvkun 2007). In addition, treatment with rapamycin, the inhibitor of TOR, extends lifespan in *C. elegans* (Robida-Stubbs et al. 2012). Reduced translation underlies the longevity caused by the inhibition of TOR signaling (Hansen et al. 2007; Pan et al. 2007). The inhibition of the translation initiation factors *ife-2*/eIF4E and *ifg-1*/eIF4G, which are predicted to be regulated by TOR, extends lifespan (Pan et al. 2007; Wang et al. 2010; Rogers et al. 2011; Hansen et al. 2007; Syntichaki et al. 2007; Curran and Ruvkun 2007). Several longevity-promoting transcription factors including *pha-4*/FoxA (Sheaffer et al. 2008), HSF-1 (Seo et al. 2013), SKN-1 (Robida-Stubbs et al. 2012), and DAF-16 (Seo et al. 2013; Robida-Stubbs et al. 2012; Hansen et al. 2007) mediate the longevity caused by reduced TOR signaling. In addition, AMP-activated protein kinase (AMPK), a nutrient-sensing and longevity-promoting kinase, is required for the extended lifespan of *rsks-1* mutants (Selman et al. 2009). Thus, reduced TORC1 signaling appears to lead to decreased translation, which in turn up-regulates various downstream longevity factors.

How does TOR signaling modulate longevity by influencing mRNA translation rates? Because protein synthesis requires large amounts of energy and metabolic resources such as ATP and amino acids, thrifty usage of proteins may be a cost-effective way for organisms to use resources for maintenance. Additionally, a slowed rate of protein synthesis may give organisms a chance to increase overall protein quality, because protein repair and degradation systems can be efficiently act on a relatively small amount of proteins. In addition to reducing translation, the inhibition of TOR signaling enhances autophagy-related processes (reviewed in Green et al. 2014). This in turn removes and/or recycles damaged proteins and organelles by selectively transporting them to lysosomes, which can promote healthy cellular environments. Thus, the inhibition of TOR signaling may benefit longevity by enhancing protein quality and reducing proteotoxicity during aging.

8.2.3 Genes That Mediate Dietary Restriction-Induced Longevity

Dietary restriction, which is defined as the restriction of food intake without malnutrition, extends lifespan in various species (reviewed in Piper et al. 2011). In *C. elegans*, diverse DR regimens have been used, such as genetic mutations that

decrease feeding rates, the dilution or deprivation of food (bacteria) concentrations, intermittent fasting, and culture in axenic media that contain sparse nutrients (summarized in Greer and Brunet 2009). Interestingly, different genes and pathways mediate the effects of diverse DR regimens on longevity in *C. elegans* (Fig. 8.2, Table 8.1). The most notable genetic factors that mediate the longevity conferred by DR are cellular energy sensors. Dietary restriction decreases ATP levels and subsequently increases the AMP/ATP ratio, and this in turn activates the energy sensor AMPK (Hardie 2014). The catalytic α subunit of AMPK in *C. elegans*, AAK-2, is necessary and sufficient for DR-induced longevity (Greer and Brunet 2009; Greer et al. 2007). Target of rapamycin (TOR), another major energy sensor, is also implicated as a mediator of DR-induced longevity (Hansen et al. 2007). The inhibition of *let-363*, *C. elegans* TOR, extends lifespan, perhaps by mimicking DR. The lifespan extension conferred by intermittent fasting is mediated by RHEB-1 (GTPase), an activator of TOR (Honjoh et al. 2009). One possible mechanism by which reduced TOR levels mediate DR-induced longevity is the up-regulation of autophagy (reviewed in Green et al. 2014), which helps cellular maintenance during DR. Thus, DR appears to increase lifespan by regulating energy sensors to maximize cellular maintenance under conditions where energy is scarce.

DR alters the activities of longevity-promoting transcription factors. The AMPK activated upon DR up-regulates DAF-16 to mediate longevity (Greer et al. 2007). Dietary restriction reduces TOR signaling, which leads to changes in the activity of transcription factors including PHA-4 (Panowski et al. 2007; Sheaffer et al. 2008), hypoxia-inducible factor 1 (HIF-1) (Chen et al. 2009), HSF-1 (Seo et al. 2013; Steinkraus et al. 2008), DAF-16 (Robida-Stubbs et al. 2012; Seo et al. 2013), and SKN-1 (Bishop and Guarente 2007; Robida-Stubbs et al. 2012). SIR-2.1 (sirtuin: NAD-dependent protein deacetylase) (Wang and Tissenbaum 2006) and PNC-1 (a key component of the NAD^+ salvage pathway) (Moroz et al. 2014) mediate DR-induced longevity. NHR-62 (nuclear receptor) mediates the lifespan-increasing effects of DR by controlling fat metabolism and autophagy (Heestand et al. 2013). WWP-1 (E3 ligase) and UBC-18 (E2 conjugating enzyme), components of the ubiquitin system, extend lifespan upon DR by degrading kruppel-like factor 1 (KLF-1) (Carrano et al. 2014; Carrano et al. 2009).

Under DR, organisms decrease their rates of growth and reproduction to preserve resources for survival until food conditions become more favorable. These maintenance responses appear to promote stress resistances and eventually lead to longevity. In *C. elegans*, various factors, including cellular energy sensors, in diverse longevity pathways mediate DR-induced longevity in a diet regimen-dependent manner. Thus, these factors may sense various DR cues and transmit longevity signals to different pathways. It will be important to dissect the mechanisms by which these diverse factors or pathways interact with each other for lifespan extension in response to DR.

8.2.4 Autophagy-Related Genes Required for Longevity

Autophagy is a process that promotes the degradation of cellular components to recycle macromolecules and organelles (reviewed in Levine and Klionsky 2004). The appropriate clearance of damaged cellular components mediated by autophagy is one of the crucial requirements for lifespan extension in *C. elegans*. Autophagy was first identified in mammals, and subsequent genetic studies using yeast identified many autophagy-related genes (ATGs). Autophagy begins with the induction of membrane changes (regulated by *unc-51/ATG1*), vesicle nucleation (regulated by *bec-1/ATG6*, *vps-34/VPS34*), vesicle expansion (regulated by *atg-7/ATG7*, *lgg-1/ATG8*, *lgg-3/ATG12*), and eventually retrieval (regulated by *atg-18/ATG18*). Those ATGs are well-conserved across species including *C. elegans*.

Many lifespan-regulating factors such as IIS, TOR, DR, and reproductive pathways have been shown to modulate autophagy in *C. elegans*. The role of autophagy in promoting longevity was first shown for reduced IIS (Melendez et al. 2003). *daf-2* mutants display increased levels of autophagy and require autophagy-related genes, including *bec-1/ATG6* and *lgg-3/APG12*, for longevity (Melendez et al. 2003; Hars et al. 2007). Acting downstream of IIS (Apfeld et al. 2004), AMPK contributes to the up-regulation of autophagy in *daf-2* mutants (Egan et al. 2011). Although DAF-16 is not required for increased autophagy in *daf-2* mutants (Hansen et al. 2008), overexpression of the DAF-16 is sufficient to induce autophagy (Jia et al. 2009).

Dietary restriction induces autophagy, and essential autophagy genes are required for the longevity caused by genetic mimesis of DR (Jia and Levine 2007; Hansen et al. 2008). Dietary restriction appears to reduce TOR signaling (reviewed in Johnson et al. 2013) and up-regulate the transcription factors PHA-4 and TFEB/*hlh-30* to mediate autophagy-induced longevity (Hansen et al. 2008; Lapierre et al. 2013a). Overall, increased autophagy is required for the longevity caused by multiple signaling pathways, most if not all of which are sensitive to nutrient conditions. Thus, autophagy may provide the nutrients and energy required for longevity pathways. Because evidence supporting the hypothesis that enhanced autophagy *per se* is sufficient for longevity is scarce, it seems likely that autophagy is a limiting factor for longevity.

8.2.5 Longevity Caused by Reduced Mitochondrial Function

Mitochondria are crucial for many physiologic processes including energy production. Interestingly, a mild inhibition of the mitochondrial electron transport chain (ETC) generally promotes longevity in *C. elegans* (Fig. 8.3) (reviewed in Hwang et al. 2012). One of the first long-lived mitochondrial ETC mutants that were identified was the *clk-1* (demethoxyubiquinone hydroxylase) mutant (Wong et al. 1995; Braeckman et al. 1999; Ewbank et al. 1997). Other long-lived ETC

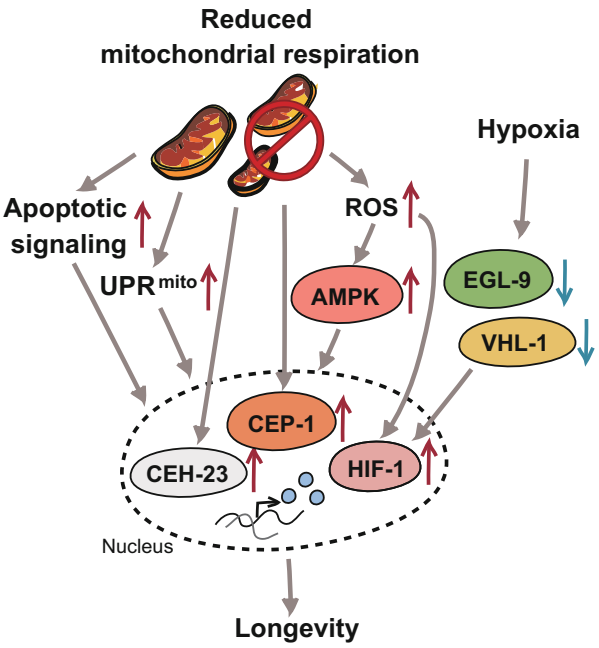

Fig. 8.3 Lifespan-regulatory pathways of reduced mitochondrial respiration and HIF-1. Impaired mitochondrial respiration extends lifespan by causing a global change in gene expression via non-mitochondrial mediators. These mediators include nuclear transcription factors, AMPK (AMP-activated protein kinase), the apoptotic signaling pathway, and the mitochondrial unfolded protein response (UPR^{mito}). In addition, increased reactive oxygen species (ROS) levels mediate longevity in respiratory mutants through AMPK and HIF-1. HIF-1 is also stabilized upon hypoxia via EGL-9 (proline hydroxylase) and VHL-1 (ubiquitin E3 ligase)

mutants include the *isp-1* (iron-sulfur protein) mutants, which are defective in mitochondrial complex III (Feng 2001), and the *nuo-6* (NADH ubiquinone oxidoreductase) mutants, which are defective in mitochondrial complex I (Yang and Hekimi 2010b). In addition, RNAi knockdown of many genes that encode mitochondrial ETC components leads to longevity (Dillin et al. 2002b; Lee et al. 2003; Hansen et al. 2005).

Several key downstream factors and signaling pathways are known to mediate the longevity of mitochondrial ETC mutants. These include FSTR-1/-2, AMPK, HIF-1, CEH-23 (homeobox domain transcription factor), the mitochondrial unfolded protein response (UPR^{mito}) genes, CEP-1 (p53 homolog), components of the apoptotic signaling pathway, and the TAF-4/TFIID complex (Baruah et al. 2014; Yee et al. 2014; Khan et al. 2013; Walter et al. 2011; Durieux et al. 2011; Lee et al. 2010; Ventura et al. 2009; Cristina et al. 2009; Curtis et al. 2006; Hwang et al. 2014). The inhibition of the ETC appears to modulate signaling from the mitochondria to other cellular organelles including the nucleus. For example, reduced mitochondrial respiration leads to changes in global gene expression, which contribute to a long lifespan (Yee et al. 2014; Cristina

et al. 2009). The global changes in gene expression appear to be mediated by transcription factors such as HIF-1 and CEP-1 (Hwang et al. 2014; Baruah et al. 2014).

Many long-lived ETC mutants display increased ROS levels, which actually contribute to longevity (Hwang et al. 2014; Lee et al. 2010; Yang and Hekimi 2010a; Van Raamsdonk and Hekimi 2012). Long-lived mitochondrial mutants have increased mitochondrial ROS levels (Yang and Hekimi 2010a; Hwang et al. 2014; Lee et al. 2010), and antioxidant treatment suppresses this longevity (Yang and Hekimi 2010a; Van Raamsdonk and Hekimi 2012). Thus, increased ROS levels seem to contribute to the long lifespan of ETC mutants. Furthermore, increased HIF-1 and AMPK activities in response to elevated ROS levels mediate this ROS-induced longevity (Hwang et al. 2014; Lee et al. 2010). These findings invite a revision of the free radical theory of aging (Harman 1956, 1972), which proposes that ROS cause aging and therefore shorten lifespan.

Another key parallel signaling pathway required for the longevity of ETC mutants is the UPR^{mito}. The UPR^{mito} is a stress response that relays signals from the mitochondria to the nucleus to induce mitochondrial chaperon proteins (reviewed in Haynes et al. 2013). Impaired ETC function in one tissue (e.g., neurons) activates the UPR^{mito} and relays yet unidentified longevity signals to other tissues (e.g., intestinal cells) to extend lifespan (Durieux et al. 2011). However, the activation of the UPR^{mito} is not sufficient to promote longevity (Bennett et al. 2014).

Since the first long-lived mitochondrial respiratory *clk-1* mutants were identified, numerous studies have been conducted to reveal the molecular mechanisms underlying this lifespan regulation. Only recently, scientists started to understand the paradox of how reduced ETC delays aging and increases lifespan. Interestingly, simple and small animal species that have high respiration rates tend to live shorter lives, whereas complex and large species with low respiration rates tend to live longer lives (reviewed in Kenyon 2010). Perhaps the longevity displayed by *C. elegans* ETC mutants mimics the evolution of longevity among species.

8.2.6 The Regulation of Lifespan by the Hypoxia-Inducible Factor 1-Regulatory Pathway

Hypoxia-inducible factor 1 (HIF-1) is a key transcription factor that regulates responses to conditions of low oxygen (Fig. 8.3) (reviewed in Powell-Coffman 2010; Semenza 2012). Under normal oxygen conditions, HIF-1 is hydroxylated by the proline hydroxylase EGL-9 and ubiquitinated by von Hippel-Lindau-1 (VHL-1), an E3 ligase component. Under conditions of low oxygen, EGL-9 cannot hydroxylate HIF-1, leading to the stabilization of HIF-1 and the induction of HIF-1 target genes. HIF-1 modulates various biological processes, including lifespan- and aging-related processes in *C. elegans*.

The up-regulation of HIF-1, by the genetic inhibition of VHL-1 or EGL-9 (Lee et al. 2010; Mehta et al. 2009; Muller et al. 2009), or by the overexpression of *hif-1*, increases lifespan (Zhang et al. 2009). The activation of HIF-1 also contributes to the longevity conferred by mitochondrial ROS in a positive-feedback fashion and through the modulation of iron-metabolism genes (Lee et al. 2010; Hwang et al. 2014). Interestingly, HIF-1 also regulates lifespan in a temperature-dependent manner, possibly through IIS (Lee et al. 2010; Leiser et al. 2011; Chen et al. 2009; Zhang et al. 2009), and mediates DR-induced longevity (Chen et al. 2009). Overall, HIF-1 appears to act as a sensor and mediator for various lifespan-regulatory signals such as oxygen concentration, mitochondrial ROS, temperature changes, and nutrient levels.

Because HIF-1 is one of the recently identified factors that regulate aging in *C. elegans*, the mechanisms by which HIF-1 increases lifespan remain elusive. Different from vertebrate models, the availability of viable *hif-1, vhl-1*, and *egl-9* mutants has made *C. elegans* a unique and important model organism to study the role of HIF-1 in aging. Future studies regarding HIF-1, including tissue-specific roles and the functional characterization of upstream and downstream factors, will provide mechanistic insights into how this evolutionarily conserved transcription factor exerts its effects on longevity.

8.2.7 Sensory Neuronal Regulation of Longevity

C. elegans is equipped with a sensory nervous system that perceives environmental changes. Intriguingly, sensory neurons modulate lifespan in *C. elegans* (Fig. 8.4), and this phenomenon is also observed in *Drosophila* and mice (Linford et al. 2011; Jeong et al. 2012; Riera et al. 2014). Structural perturbations of a subset of ciliated sensory neurons, including the genetic disruption of *che-2*/*IFT80*, *daf-10*/*IFT122*, *daf-19*/*RFX2*, or *osm-5*/*IFT88*, increase lifespan in *C. elegans* (Apfeld and Kenyon 1999; Alcedo and Kenyon 2004). Many *C. elegans* mutants that have defects in sensory signal transduction also live long. The genetic inhibition of *str-2*, a putative sensory G protein-coupled receptor, or of *kin-29* (SIK3 kinase), which regulates the expression of subsets of neuronal sensory receptors, lengthens lifespan (Lanjuin and Sengupta 2002; Alcedo and Kenyon 2004). The inhibition of G proteins that act downstream of sensory receptors such as *gpa-1*, *gpa-5*, *gpa-9*, and *odr-3* extends lifespan as well (Lans and Jansen 2007; Alcedo and Kenyon 2004). The genetic modulation of downstream cation channels, including *tax-4* (cyclic nucleotide-gated channel subunit), *ocr-2* and *osm-9* (neuronal transient receptor potential vanilloid (TRPV) channels), and cold-sensitive *trpa-1* (TRPA channel), can increase lifespan (Apfeld and Kenyon 1999; Lee and Ashrafi 2008; Lee and Kenyon 2009; Xiao et al. 2013; Riera et al. 2014). Thus, the inhibition of the sensory neural structure or function generally increases lifespan in *C. elegans*.

The longevity caused by sensory impairment appears to be mediated at least partly by the IIS pathway. Defects in sensory neurons promote the nuclear

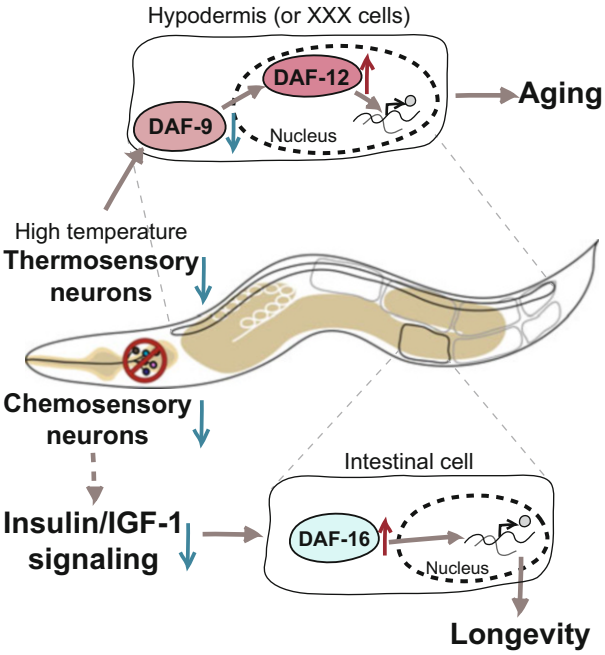

Fig. 8.4 Pathways that act downstream of sensory neurons to modulate lifespan. The inhibition of thermosensory neurons decreases *C. elegans* lifespan at high temperature (25 °C) by decreasing the expression of DAF-9 (cytochrome P450) in distal tissues such as hypodermis and XXX cells, resulting in the activation of DAF-12 (nuclear receptor). The perturbation of chemosensory neurons presumably decreases insulin/IGF-1 signaling, which promotes the nuclear localization and activation of DAF-16/FOXO to enhance longevity

localization and transcriptional activation of DAF-16 (Lin et al. 2001; Xiao et al. 2013; Gaglia et al. 2012). In addition, the long lifespans caused by sensory mutations are largely suppressed by *daf-16* mutations (Apfeld and Kenyon 1999; Hahm et al. 2009; Lanjuin and Sengupta 2002; Lee and Ashrafi 2008; Xiao et al. 2013; Alcedo and Kenyon 2004; Lans and Jansen 2007). Thus, the disruption of sensory neurons increases lifespan in *C. elegans* through the activation of DAF-16. In addition, the long lifespan of sensory *daf-10/IFT122* mutants requires the induction of *mct-1*, a putative monocarboxylate transporter (Gaglia et al. 2012). This suggests that the transportation of hormones or small molecules modulates lifespan by acting downstream of the sensory perturbation. In contrast to these long-lived sensory mutants, which mostly have chemosensory defects, mutants that have defects in thermosensory AFD neurons are short lived at high temperatures (25 °C) (Lee and Kenyon 2009). This lifespan regulation is mediated by steroid signaling, composed of DAF-9 (cytochrome P450) and DAF-12 (nuclear receptor) in multiple tissues, including hypodermis and endocrine XXX cells (Lee and Kenyon 2009). How these various sensory modalities affect lifespan by employing different downstream factors is currently unclear.

It is intriguing that the inhibition of a small number of sensory neurons can have a large effect on the organismal lifespan. Several signaling pathways that regulate aging, including those involved in IIS, TOR, DR, and autophagy, are concerned with nutrient and food availability. Because foods have smells and tastes as well as nutrients, the sensory neurons may be an intrinsic factor that acts at the upstream end of longevity signaling pathways that are linked with food availability. In fact, sensory cues can directly influence lifespan via sensory neurons in *C. elegans* and *Drosophila* (Libert et al. 2007; Maier et al. 2010). Hence, one can speculate that sensory neurons monitor environmental changes such as food availability and temperature fluctuations and modulate physiologic processes that eventually affect lifespan.

8.2.8 *Lifespan Regulation by the Reproductive System*

Organismal longevity is frequently associated with reduced reproduction. In *C. elegans*, the removal of the germline promotes longevity (Fig. 8.5) (Hsin and Kenyon 1999). This phenomenon does not result from a simple trade-off between longevity and reproduction, because the removal of the somatic gonad together with germline does not result in longevity (Hsin and Kenyon 1999). Instead, when the

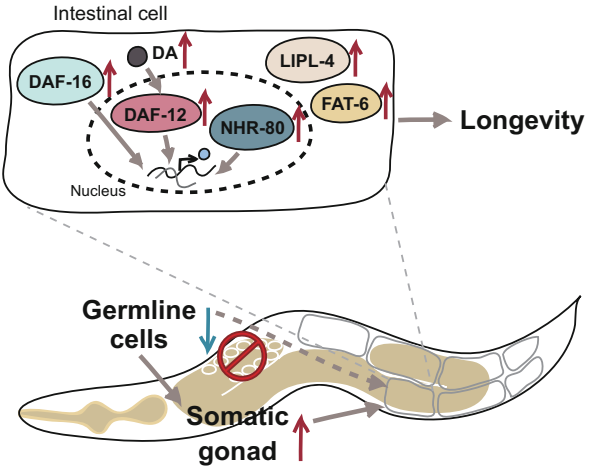

Fig. 8.5 The components of the reproductive system, which regulates longevity. The removal of germline cells increases lifespan by transmitting longevity signals from the somatic gonad to intestinal cells in *C. elegans*. This gonadal signaling increases the synthesis of dafachronic acid (DA), which results in the activation of DAF-12 (nuclear receptor). In addition, signals from the gonad enhance the nuclear localization and transcriptional activity of DAF-16/FOXO. Moreover, the gonadal signaling modulates fat metabolism by up-regulating the NHR-49, 80 (nuclear receptors: NHRs) and LIPL-4 (lipase) to promote longevity

germline is removed, the somatic gonad actively promotes longevity by sending signals that modulate steroid signaling, DAF-16 activities, and fat metabolism.

The DAF-12 is one of the key components in steroid signaling (Antebi et al. 2000) and is required for longevity in germline-ablated worms (Hsin and Kenyon 1999). The activity of DAF-12 is regulated by dafachronic acids (DAs), which are bile acid-like steroid ligands (Motola et al. 2006). DAs are synthesized from cholesterol by multiple enzymatic components such as DAF-36 (Rieske-like oxygenase), DHS-16 (3-hydroxysteroid dehydrogenase), and DAF-9 (Rottiers et al. 2006; Wollam et al. 2012; Jia et al. 2002; Gerisch et al. 2001). Those components, as well as DAs, contribute to the longevity induced by the lack of the germline resulting from laser ablation or *glp-1* (germ line proliferation 1) mutations. For example, mutations in *daf-36*, *dhs-16*, or *daf-9* suppress the long lifespan induced by the lack of germ cells (Rottiers et al. 2006; Wollam et al. 2012; Gerisch et al. 2001). Dafachronic acids are ligands of DAF-12 that promote lifespan extension in animals lacking germline cells (Gerisch et al. 2007; Yamawaki et al. 2010; Mahanti et al. 2014), although treatment with DAs is not sufficient to increase lifespan in wild-type worms (Gerisch et al. 2007; Yamawaki et al. 2010). Thus, the loss of the germline leads to the production of high levels of DAs in the somatic gonad, which activate DAF-12 and promote longevity.

Another component that mediates the longevity conferred by germline loss is DAF-16, which is activated by germline loss and is required for the lifespan extension associated with germline loss (Hsin and Kenyon 1999; Lin et al. 2001). Upon germline removal, intestinal DAF-16 translocates from the cytosol to the nucleus (Lin et al. 2001). This process is mediated by DAF-9, DAF-12, and KRI-1/KRIT1/CCM1, independently of IIS (Berman and Kenyon 2006). Moreover, the transcriptional activity of nuclear DAF-16 is regulated by several factors such as TCER-1/TCERG-1, PHI-62 (a predicted RNA-binding protein), and FTT-2/14-3-3 (Ghazi et al. 2009; McCormick et al. 2012). Thus, the loss of the germline enhances the transcriptonal activity of DAF-16 to induce longevity genes and increases lifespan.

Fat metabolism also plays key roles in the regulation of lifespan by the reproductive system. Oil red O fat staining and Coherent Anti-Stokes Raman Scattering (CARS) microscopy indicate that germline loss increases fat storage (O'Rourke et al. 2009; Lapierre et al. 2013b). Moreover, several factors that regulate fat metabolism are required for the longevity conferred by germline loss, including NHR-49 and NHR-80, nuclear receptors that regulate fat metabolism (Goudeau et al. 2011; Ratnappan et al. 2014). The gonadal signaling is also mediated by the induction of *lipl-4* (a triglyceride lipase) that functions to increase lifespan (Wang et al. 2008; Lapierre et al. 2011). Thus, changes in fat metabolism contribute to the extension of lifespan by germline loss.

In *C. elegans*, the somatic gonad seems to relay longevity signals to other body parts upon sensing the loss of the germline. When the germ cells are compromised, the somatic gonad sends signals that may help the survival of the soma, and the animals may resume reproduction under conditions that favor reproduction. This may help the animals balance the whole system between the maintenance of somatic health and the promotion of reproduction. Interestingly, the regulation of

lifespan by the reproductive system is also observed in other species, including *Drosophila* (Flatt et al. 2008) and mice (Cargill et al. 2003). Thus, the elucidation of the mechanisms by which the reproductive system regulates longevity will provide useful information regarding how reproduction and aging have evolved in an interlocked manner in complex organisms such as humans.

8.3 Conclusions

In this chapter, we reviewed representative pathways and genes that influence longevity in *C. elegans*. More than 20 years of research using *C. elegans* has provided invaluable information about the genetics of aging. Importantly, many of the genes that regulate aging in *C. elegans* are implicated in the longevity of mammals, including humans. For example, the identification of IIS as a longevity pathway in *C. elegans* has led the way for the discovery of *FOXO3A* variants in long-lived humans. In addition, the dissection of TOR signaling as a target of anti-aging medicine has helped the emergence of rapamycin as a lifespan-extending drug in mice (Harrison et al. 2009). Overall, it is indisputable that the aging research using *C. elegans* has provided pivotal clues to the basis for slowing human aging and delaying the onset of age-related diseases.

Organismal lifespan is highly plastic and subject to changes in environmental and internal conditions. Under normal conditions, lifespan-regulatory pathways support growth, reproduction, and other essential cellular functions such as translation and energy production. However, under harsh conditions, including low food availability and the presence of various stressors, those pathways appear to shift from growth and reproduction to protective states, which eventually lead to longevity. For example, a reduction in food availability alters the function of multiple lifespan-regulatory pathways, including TOR, IIS, and autophagy, to promote longevity. The loss of the germline extends lifespan, likely by sending longevity signals from the reproductive organs to other body parts to support the health of somatic tissues. Decreases in sensory perception can extend lifespan, probably by transmitting cues for environmental stresses, including low food availability, into internal longevity signals. These examples can help us to interpret how organisms switch their physiologic status between growth/reproduction and maintenance/protection at the molecular level upon changes in extrinsic and intrinsic conditions.

Many of the genes and pathways described in this chapter have emerged as promising targets for anti-aging medicine. However, most of these pathways are tightly linked to one another. Hence, it will be difficult to predict the exact physiologic outcome of intervention in one pathway, which may lead to alterations in the function of other vital pathways. In this regard, a major challenge in aging research may be to unravel the complex network among the lifespan-regulatory pathways. In addition, some factors that increase longevity come with expenses including reduced fitness. Therefore, it will be important to uncouple the longevity from adverse side effects by elucidating precise mechanisms. Because many of the

pathways that regulate aging are evolutionarily conserved, findings regarding *C. elegans* longevity genes will likely impact on aging research in mammals as well. Thus, deciphering the whole network among these pathways and genes in *C. elegans* will eventually help us to achieve longer and healthier lifespans in humans.

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