Gut Microbiota Regulate Host Longevity

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Outline

Background of longevity

Gut microbiota & Longevity

Applications

Global increase of aged population

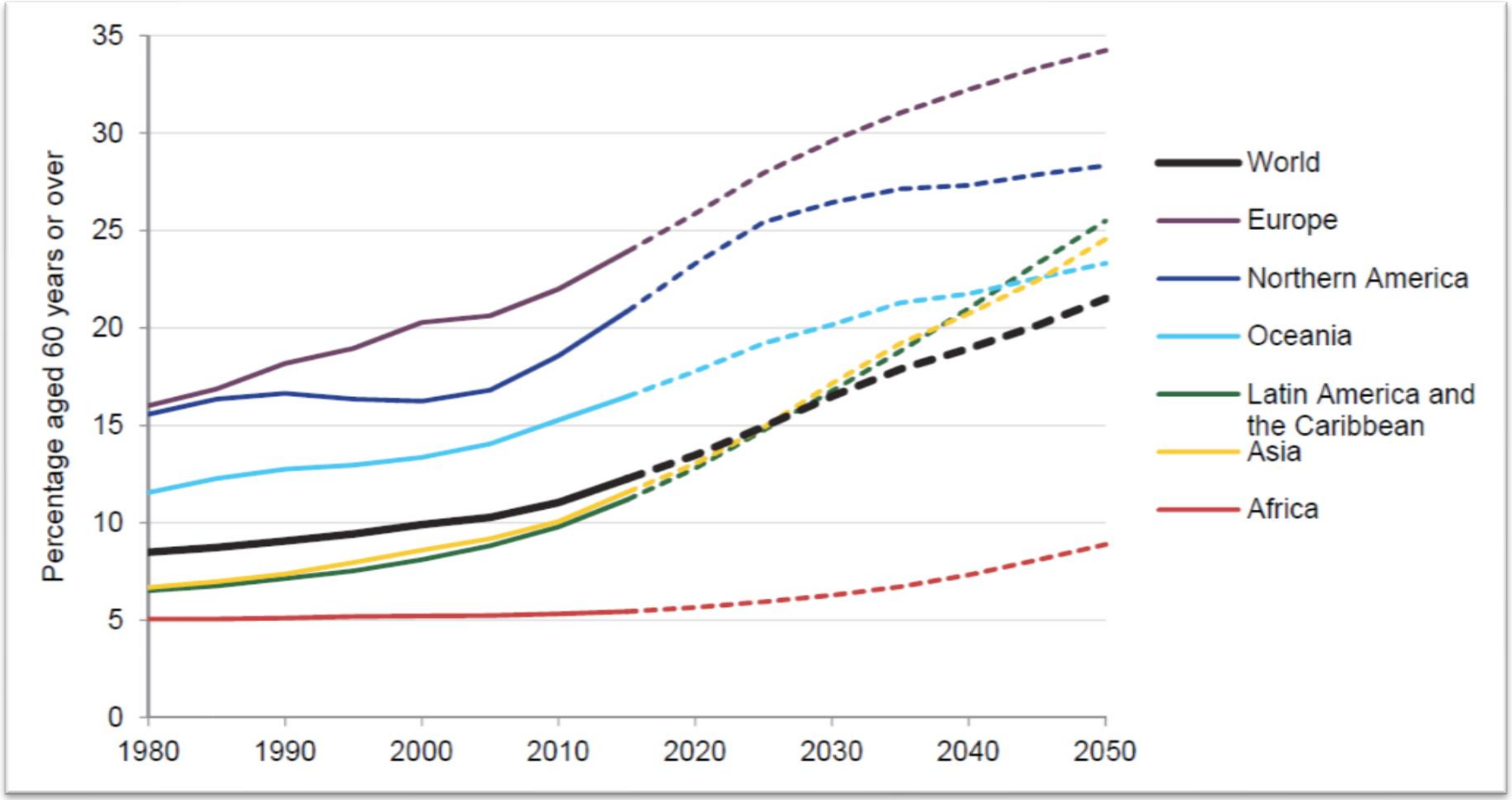


Figure 1 | Percentage of the population aged 60 years or over for the world and regions, 1980-2050

United Nations (2015). World Population Prospects: The 2015 Revision.

Aging-related diseases

	Males			Females		
	Cause of death	Deaths (thousands)	Pct	Cause of death	Deaths (thousands)	Pct
1	Ischaemic heart disease	2 985 226	17.8	Stroke	3 102 405	18.6
2	Stroke	2 614 535	15.6	Ischaemic heart disease	3 087 753	18.5
3	COPD[i]	1 541 208	9.2	COPD[i]	1 225 348	7.4
4	Lung cancer[ii]	858 088	5.1	Lower respiratory infections	780 539	4.7
5	Lower respiratory infections	746 789	4.5	Diabetes mellitus	656 592	3.9
6	Diabetes mellitus	500 976	3.0	Hypertensive heart disease	571 320	3.4
7	Hypertensive heart disease	399 580	2.4	Alzheimer's disease[iii]	455 616	2.7
8	Stomach cancer	353 508	2.1	Lung cancer[ii]	389 966	2.3
9	Prostate cancer	309 168	1.8	Breast cancer	286 593	1.7
10	Liver cancer	306 859	1.8	Kidney diseases	279 398	1.7

Figure 2 | Ten leading causes of death of those aged 60 years or over globally, by sex, 2000-2012

Data source: World Health Organization (2014). Global Health Estimates 2014 Summary Tables: Deaths by Cause, Age and Sex.2000-2012.

Gut microbiota increase host lifespan

OPINION ARTICLE

Gut microbiota as a candidate for lifespan extension: an ecological/evolutionary perspective targeted on living organisms as metaorganisms

E. Ottaviani · N. Ventura · M. Mandrioli · M. Candela · A. Franchini · C. Franceschi

OPEN ACCESS Freely available online PLoS one

Longevity in Mice Is Promoted by Probiotic-Induced Suppression of Colonic Senescence Dependent on Upregulation of Gut Bacterial Polyamine Production

Mitsuharu Matsumoto[1,2]*, Shin Kurihara[3,4], Ryoko Kibe[2], Hisashi Ashida[4], Yoshimi Benno[2]

1 Dairy Science and Technology Institute, Kyodo Milk Industry Co. Ltd., Tokyo, Japan, 2 Benno Laboratory, Innovation Center, RIKEN, Wako, Japan, 3 Division of Applied Biology, Graduate School of Science and Technology, Kyoto Institute of Technology, Kyoto, Japan, 4 Division of Integrated Life Science, Graduate School of Biostudies, Kyoto University, Kyoto, Japan

AP&T Alimentary Pharmacology

Synbiotic consumption changes the metabolism and composition of the gut microbiota in older people and modifies inflammatory processes: a randomised, double-blind, placebo-controlled crossover study

S. Macfarlane*, S. Cleary*, B. Bahrami*, N. Reynolds† & G. T. Macfarlane*

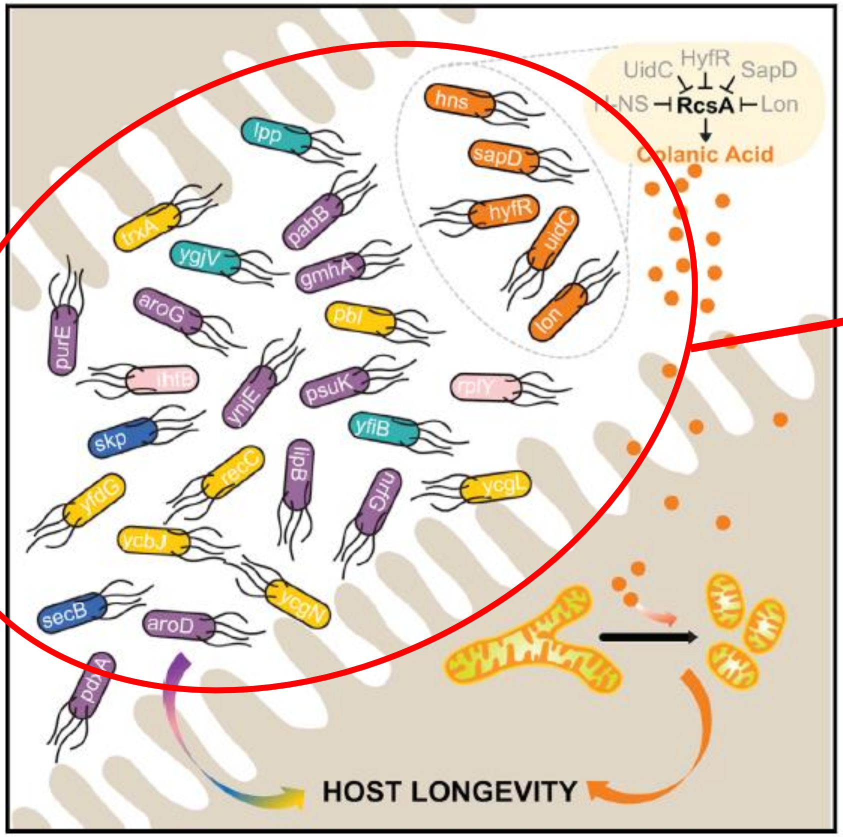
Gut microbiota increase host lifespan

Article

Cell

Microbial Genetic Composition Tunes Host Longevity

Graphical Abstract



Authors

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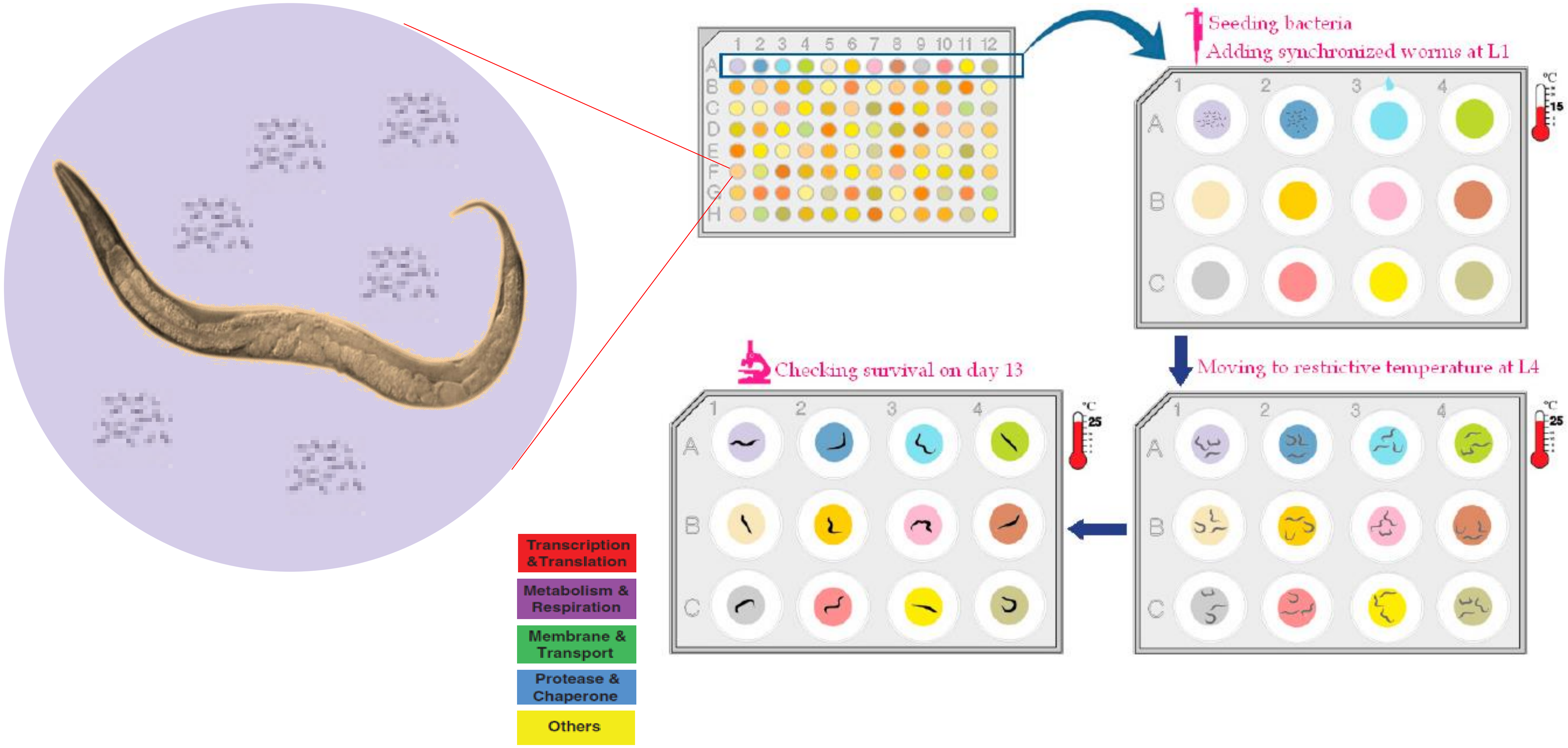
In Brief

The genetic composition of gut microbes controls the production of metabolites that impact host longevity.

genome-wide screen of the E. coli single-gene knockout library for lifespan extension in C. elegans.

Gut microbiota increase C. elegan lifespan



Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.

Gut microbiota increase C. elegan lifespan

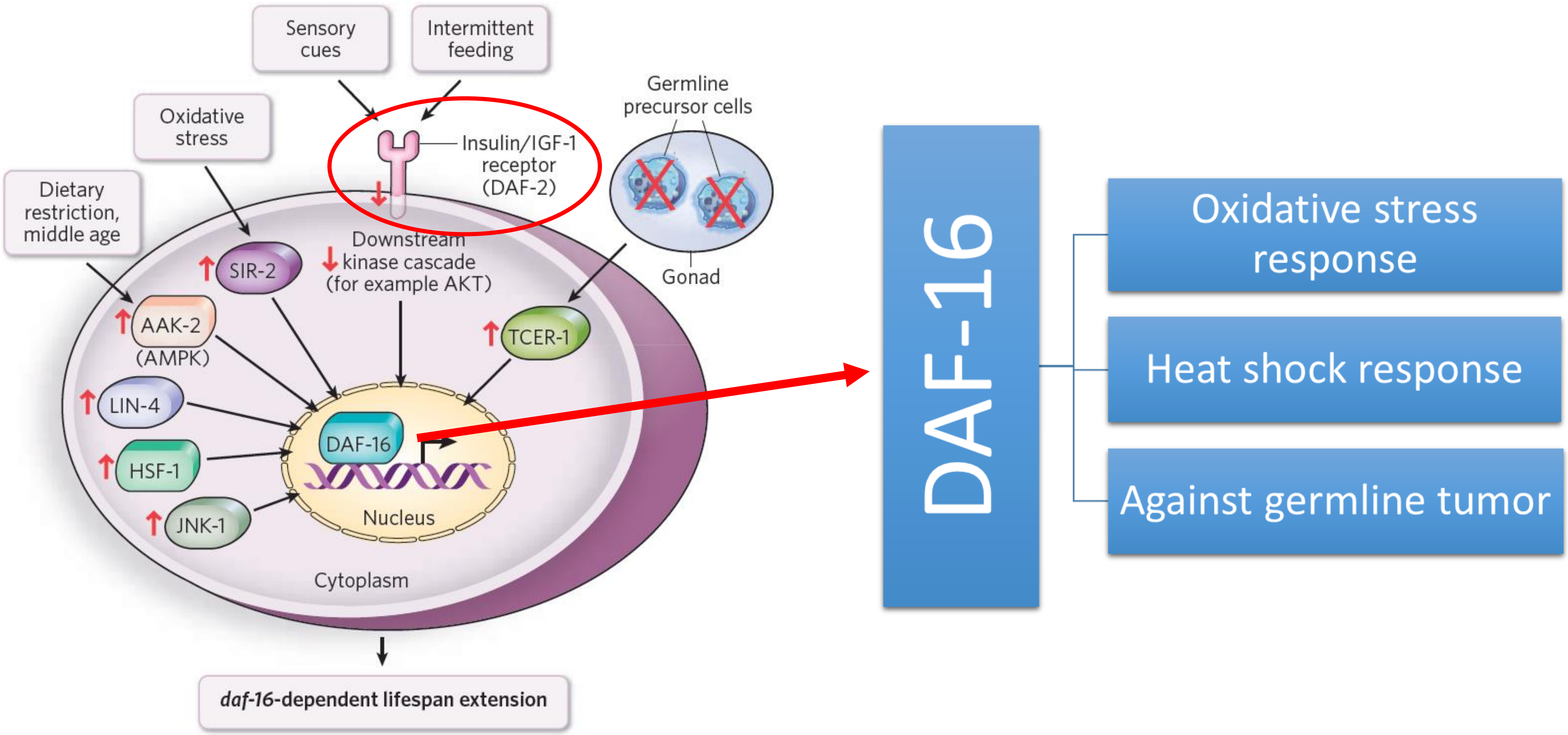
Category	Gene	Description	Lifespan Extension	*E. coli* BW25113	*E. coli* MG1655	Adult Effect
Transcription &Translation	*hns*	global DNA-binding transcriptional dual regulator	40%	Y	Y	Y
	ihfB	integration host factor; DNA-binding protein	35%	Y	Y	Y
	hyfR	DNA-binding transcriptional activator	16%	Y	Y	Y
	rplY	50S ribosomal subunit protein	11%	Y	Y	N
Metabolism & Respiration	*aroG*	3-deoxy-D-arabino-heptulosonate-7-phosphate synthase	29%	Y	Y	Y
	aroD	3-dehydroquinate dehydratase	24%	Y	Y	N
	lipB	lipoyl-protein ligase	23%	Y	Y	Y
	purE	N5-carboxyaminoimidazole ribonucleotide mutase	21%	Y	Y	Y
	pdxA	4-hydroxy-L-threonine phosphate dehydrogenase	21%	Y	Y	Y
	*gmhA**	D-sedoheptulose 7-phosphate isomerase	19%	Y	N/A	N/A
	pabB	aminodeoxychorismate synthase	18%	Y	Y	N
	ynjE	thiosulfate sulfur transferase	18%	Y	Y	Y
	nrfG	heme lyase	17%	Y	Y	Y
	psuK	pseudouridine kinase	10%	Y	N	N
Membrane & Transport	*lpp*	murein lipoprotein	27%	Y	Y	Y
	yfiB	outer membrane lipoprotein	20%	Y	N	N
	sapD	antimicrobial peptide transporter	17%	Y	Y	Y
	uidC	outer membrane porin protein	17%	Y	N	Y
	ygjV	inner membrane protein	12%	Y	Y	Y
Protease & Chaperone	*secB*	protein export chaperone	29%	Y	Y	Y
	lon	DNA-binding ATP-dependent protease	25%	Y	Y	Y
	skp	periplasmic chaperone	16%	Y	Y	Y
Others	*pbl*	lytic transglycosylase	21%	Y	N	N
	ycbJ	unknown	19%	Y	Y	Y
	trxA	thioredoxin	15%	Y	Y	Y
	ycgL	unknown	14%	Y	Y	N
	ycgN	unknown	12%	Y	N	Y
	recC	exonuclease V	11%	Y	Y	Y
	yfdG	prophage; bactoprenol-linked glucose translocase	10%	Y	Y	Y

Fig 4. A genome-wide screen of the E. coli single-gene knockout library for lifespan extension in C. elegans

29 out of 3983 mutants that prolong C. elegans lifespan by >10%. These mutants are classified into different functional categories, delineated by different colors.

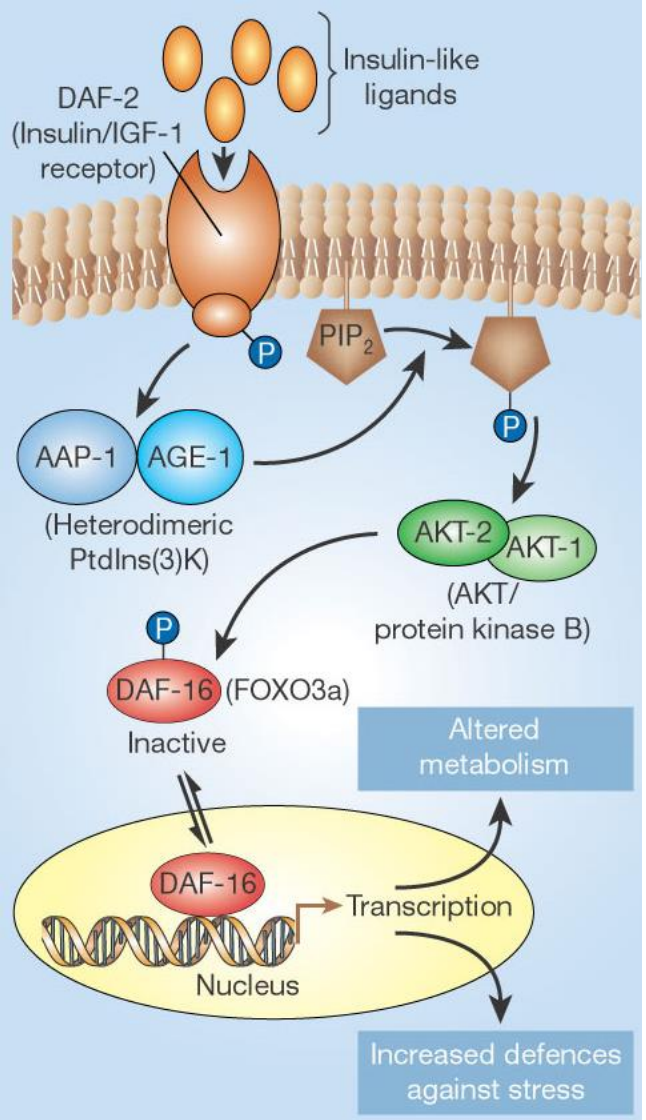
Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.

DAF-16/FOXO promotes longevity



Kenyon, C. J. (2010). The genetics of ageing. *Nature*, *464*(7288), 504-512.

The DAF-16 signalling pathway and lifespan



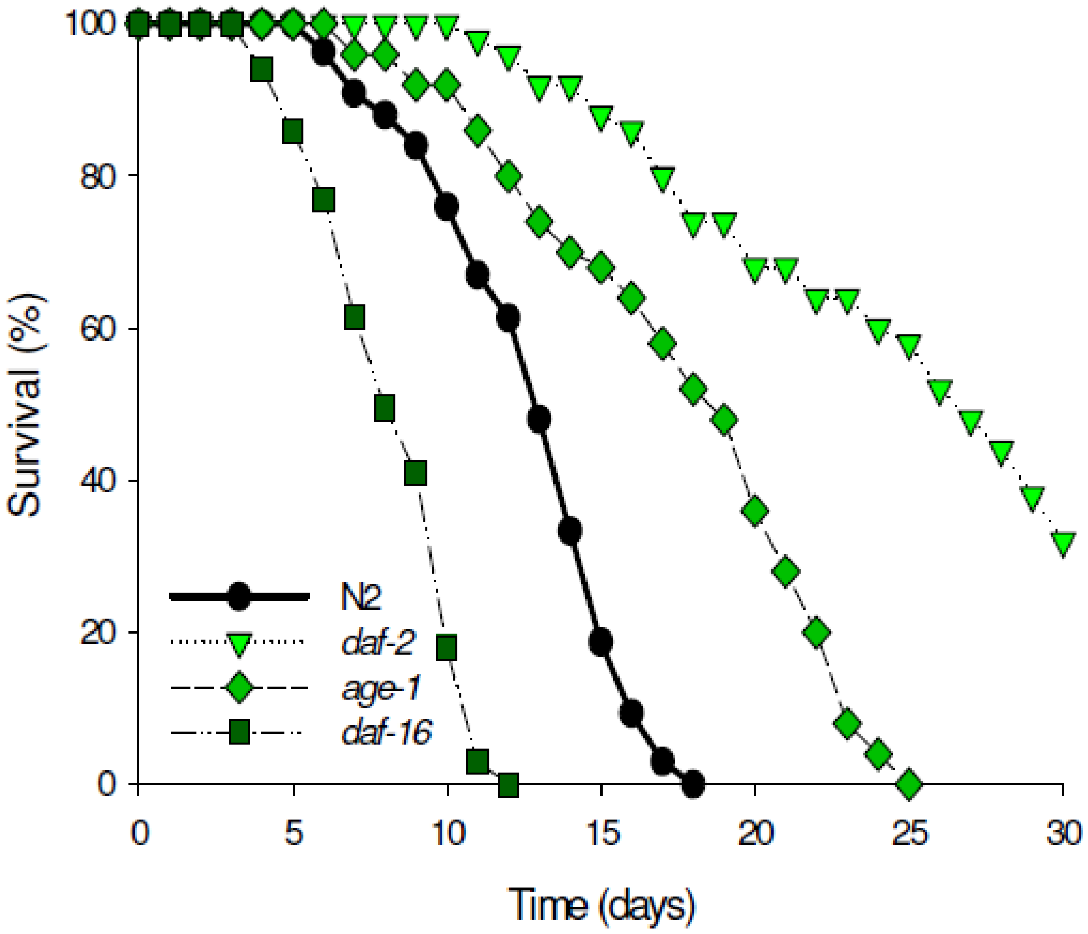


Fig 5. Survival of N2 C. elegans and DAF-2 pathway mutants grown on E. coli

Nemoto, S., & Finkel, T. (2004). *Nature*, *429*(6988), 149-152.

Portal-Celhay, C., & Blaser, M. J. (2012). *BMC microbiology*, *12*(1), 49.

Gut microbiota alters host lifespan via DAF-16

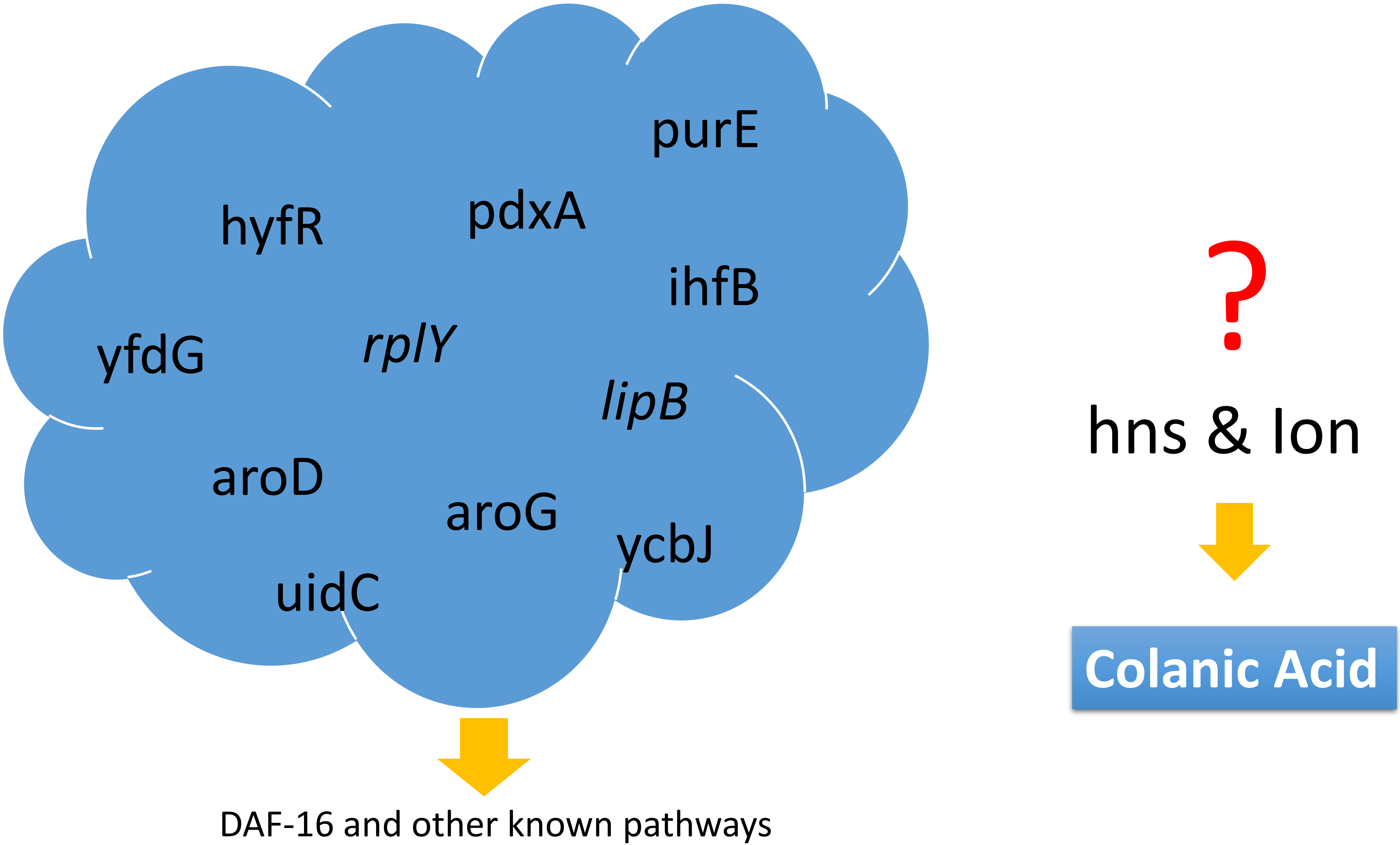
Mutant	*daf-16(mgDf47)*			
	Total N (censor N)	Lifespan extension	p value	(c
lon	167 (11)	22%	<0.001	
hns	155 (13)	17%	<0.001	
ihfB	212 (8)	29%	<0.001	
aroD	186 (7)	20%	<0.001	
secB	161 (10)	15%	<0.001	
gmhA	191 (6)	13%	<0.001	
ycgL	187 (9)	15%	<0.001	
hyfR	227 (10)	17%	<0.001	
uidC	165 (14)	15%	<0.001	
sapD	209 (5)	11%	<0.001	
ycbJ	173 (1)	21%	<0.001	
yfiB	219 (12)	17%	<0.001	
ygjV	180 (4)	14%	<0.001	
purE	151 (15)	10%	<0.001	
nrfG	218 (11)	10%	0.001	
aroG	193 (5)	19%	<0.001	
pbl	204 (2)	19%	<0.001	
lpp	180 (6)	5%	0.008	
pdxA	187 (10)	6%	0.003	
lipB	158 (12)	8%	0.001	
ynjE	203 (13)	5%	0.022	
pabB	172 (4)	8%	<0.001	
trxA	159 (15)	1%	0.419	
recC	150 (12)	4%	0.293	
skp	167 (9)	4%	0.057	
rplY	163 (7)	4%	0.094	
yfdG	161 (9)	3%	0.235	
ycgN	157 (13)	4%	0.036	
psuK	208 (13)	2%	0.358	

- Lifespan extension ≥ 10%, *p<0.05*
- Lifespan extension 5%~10%, *p<0.05*
- Lifespan extension <5%, *p>0.05*

7/29 mutants can prolong the lifespan through the host DAF-2/IGF-1 signaling pathway.

Fig 6. Genetic Interaction Analyses with Host Longevity Mechanisms

Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.


purE
hyfR
pdxA
ihfB
yfdG
rplY
lipB
aroD
aroG
ycbJ
uidC
DAF-16 and other known pathways
?
hns & lon
Colanic Acid

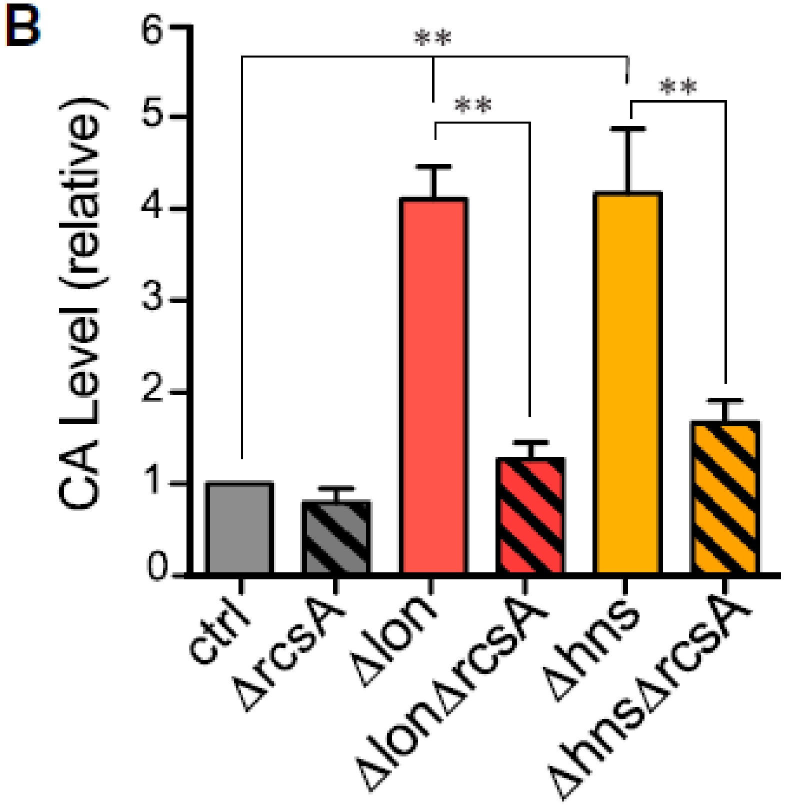


Fig 7. lon and hns show increased CA secretion in the culture medium

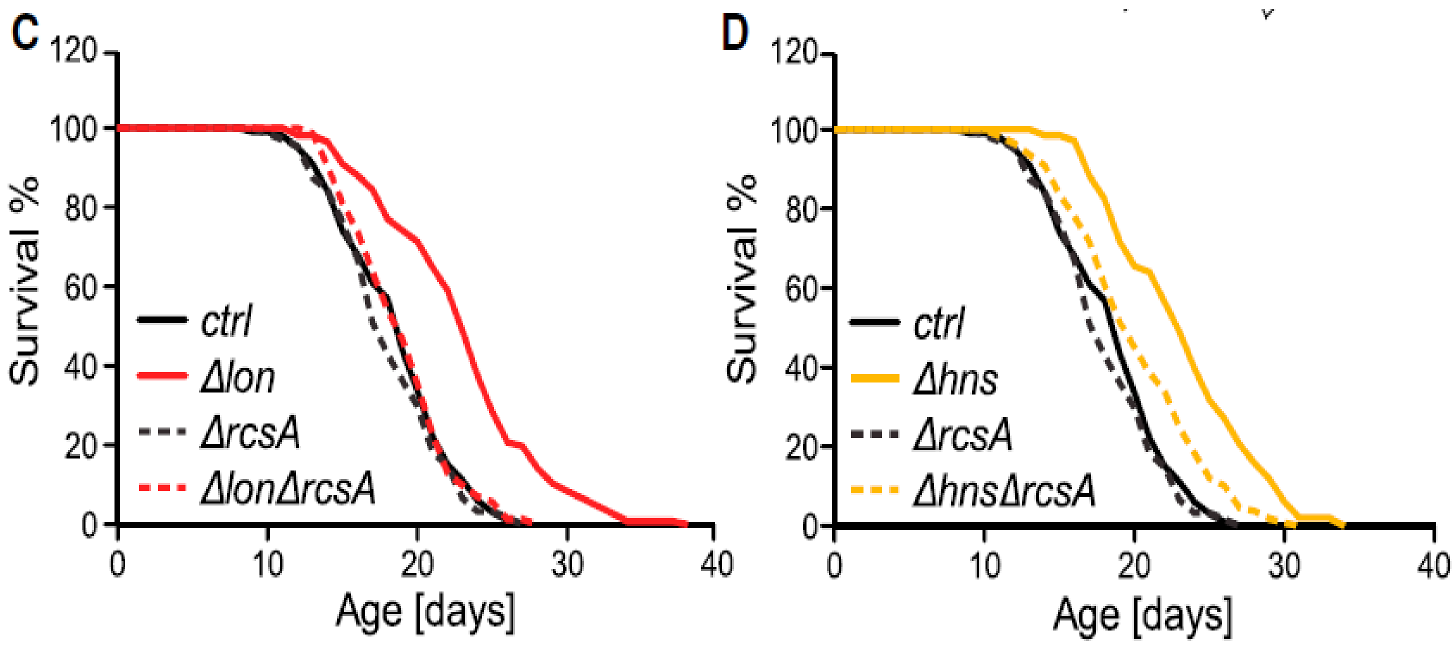


Fig 8. The rcsA deletion suppresses the lifespan extension conferred by lon and hns

Colanic Acid(CA) Overproduction as a Longevity-Promoting Mechanism

Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.

CA reduces mitochondrial fragmentation

Mitochondrial fragmentation

↓

Volume loss

↓

Shorten lifespan

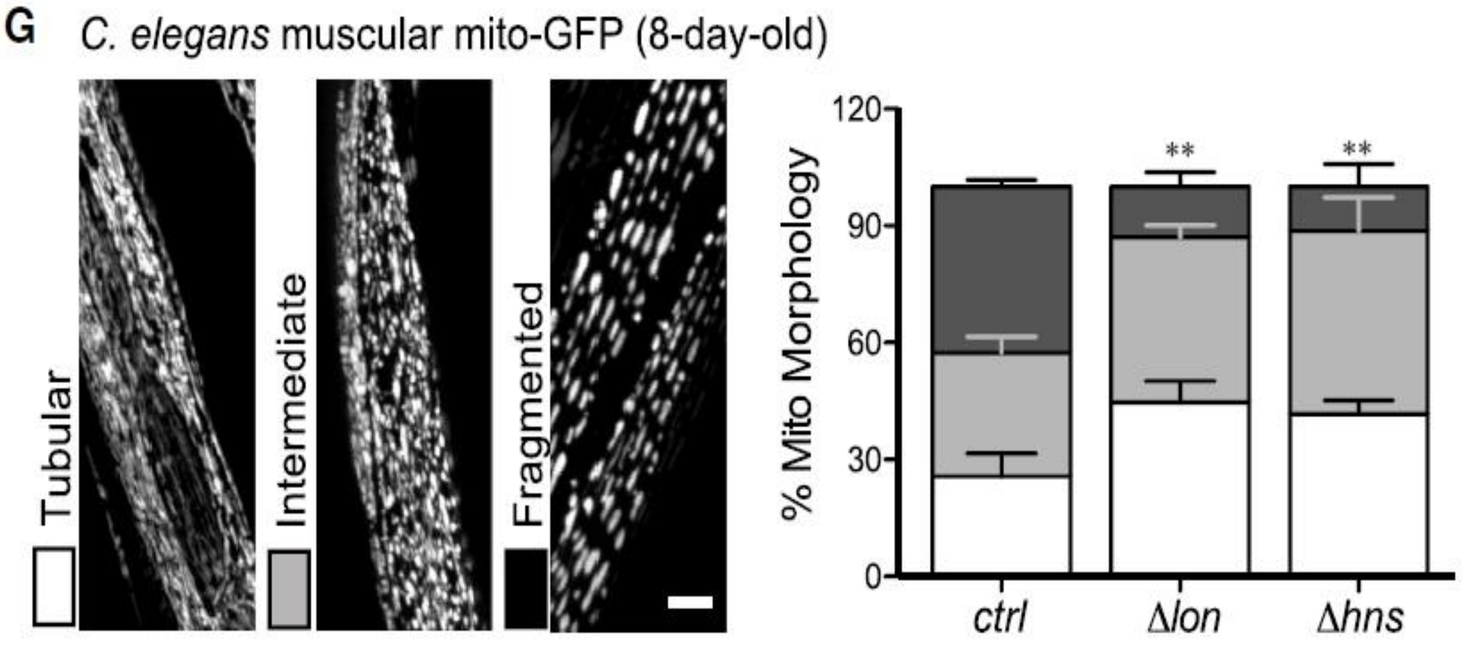
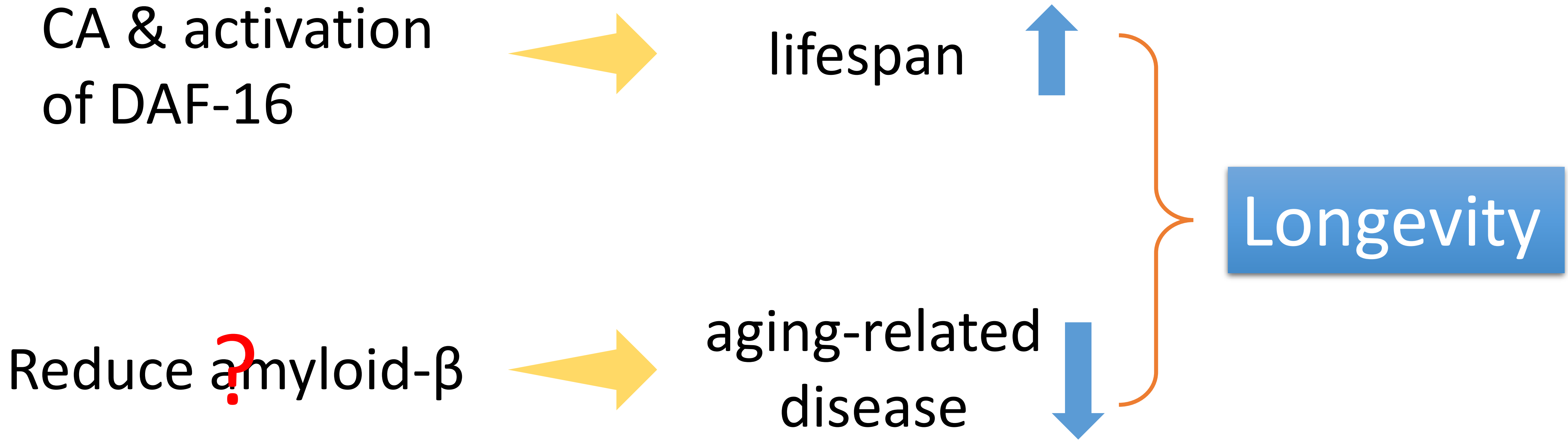


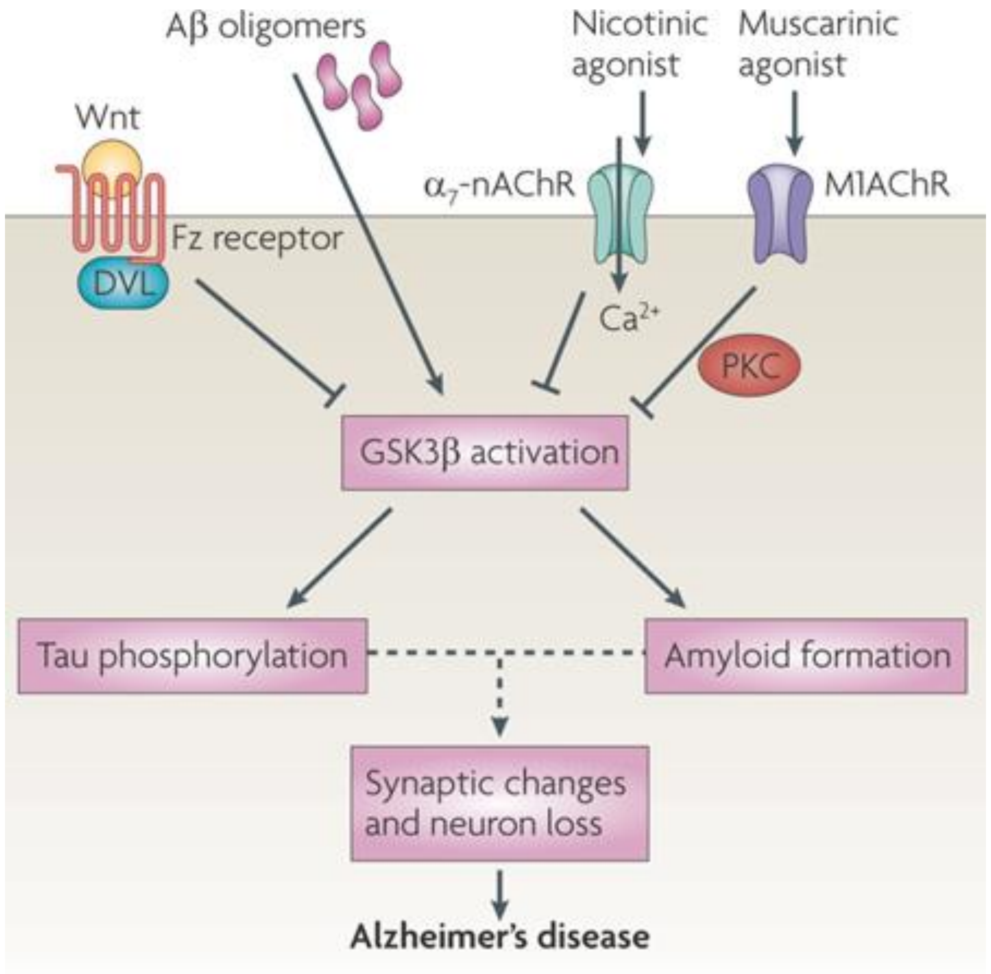
Fig 9. CA decreases mitochondrial fragmentation in C. elegans

Regmi, S. G., & Conradt, B. (2014). *Aging (Albany NY)*, *6*(2), 118.

Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.


CA & activation of DAF-16
lifespan
Reduce amyloid-β
?
aging-related disease
Longevity

Amyloid-β & Alzheimer's disease

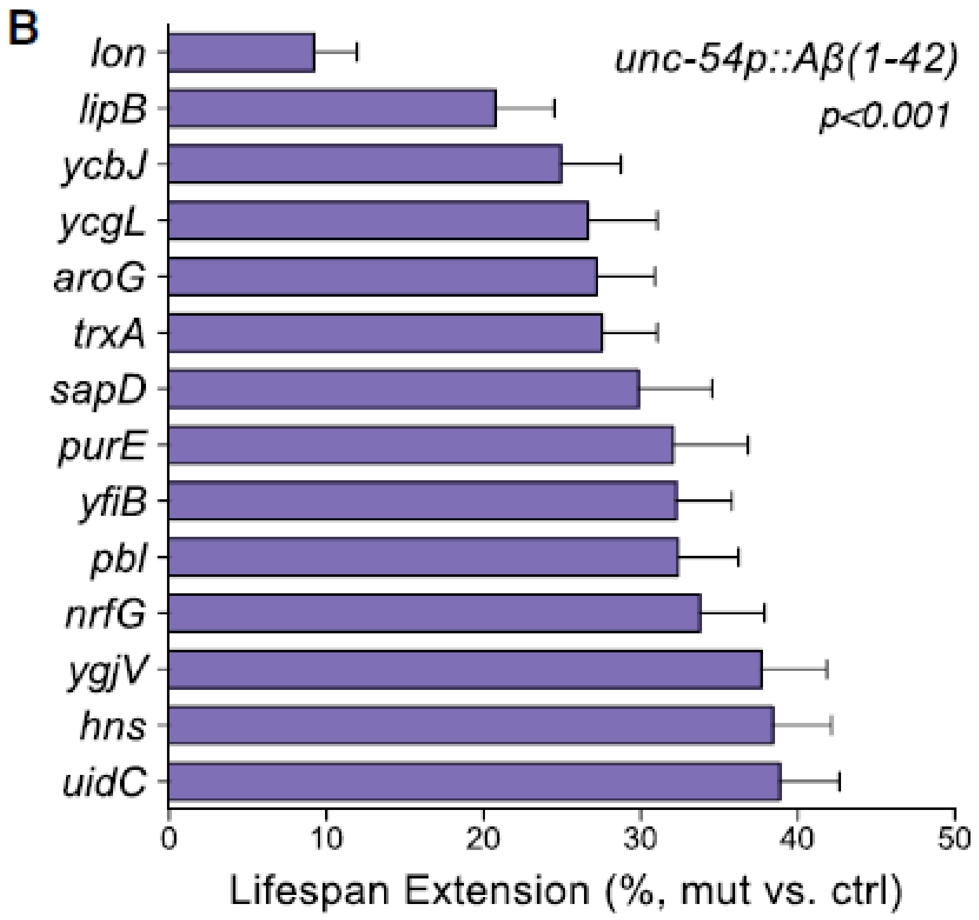


Activation of Wnt signalling protects from amyloid toxicity

-Normal: Wnt ligands inhibit GSK3β activation

-Abnormal: GSK3β is activated

Inestrosa, N. C., & Arenas, E. (2009). *Nature Reviews Neuroscience*, 11(2), nrn2755.



Fourteen bacterial mutants significantly increase the survival of Aβ transgenic strains

Fig 10. 14 mutants significantly prolong the lifespan of the Aβ transgenic strains

Microbiota ameliorates amyloid-β accumulation

Han, B., et al. (2017). *Cell*, *169*(7), 1249-1262.

Other longevity-related bacteria

Aging Cell (2016) **15**, pp227–236 Doi: 10.1111/acel.12431

Effects and mechanisms of prolongevity induced by *Lactobacillus gasseri* SBT2055 in *Caenorhabditis elegans*

OPEN ACCESS Freely available online
PLOS ONE

Anti-Inflammatory *Lactobacillus rhamnosus* CNCM I-3690 Strain Protects against Oxidative Stress and Increases Lifespan in *Caenorhabditis elegans*

Gianfranco Grompone[1,2]*, Patricia Martorell[3], Silvia Llopis[3], Núria González[3], Salvador Genovés[3], Ana Paula Mulet[2], Tamara Fernández-Calero[4], Inés Tiscornia[5], Mariela Bollati-Fogolín[5], Isabelle Chambaud[1], Benoit Foligné[6], Agustín Montserrat[7], Daniel Ramón[3]

SCIENTIFIC REPORTS
OPEN
d: 9 February 2017
d: 3 July 2017
ed online: 07 August 2017

The Transcription Factor DAF-16 is Essential for Increased Longevity in *C. elegans* Exposed to *Bifidobacterium longum* BB68

Liang Zhao[1,2], Yang Zhao[2,3], Ruihai Liu[4], Xiaonan Zheng[2,3], Min Zhang[5], Huiyuan Guo[1,2], Hao Zhang[1,3] & Fazheng Ren[1,2,3,6]

Potential application in future

Aging Cell (2015) 14, pp707–709 Doi: 10.1111/acel.12340

SHORT TAKE

The life-extending effect of dietary restriction requires Foxo3 in mice

NIH Public Access

Author Manuscript

Circ Res. Author manuscript; available in PMC 2014 March 29.

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Circ Res. 2013 March 29; 112(7): 992–1003. doi:10.1161/CIRCRESAHA.112.300749.

Expanded Granulocyte/Monocyte Compartment in Myeloid-Specific Triple Foxo Knockout Increases Oxidative Stress and Accelerates Atherosclerosis in Mice

We may utilize gut microbiota –related pathways to increase our lifespan and improve health & life quality

Summary

- Gut microbiota increase lifespan through DAF-16 pathway
- E. Coli slows aging process via colanic acid overproduction
- Gut microbiota can reduce amyloid-β accumulation

Tips of keeping healthy

1. Eat more fermented food
2. Take a probiotic supplement
3. Reduce the use of antibiotics
4. Keep regular time table & exercise more

Thanks for listening!