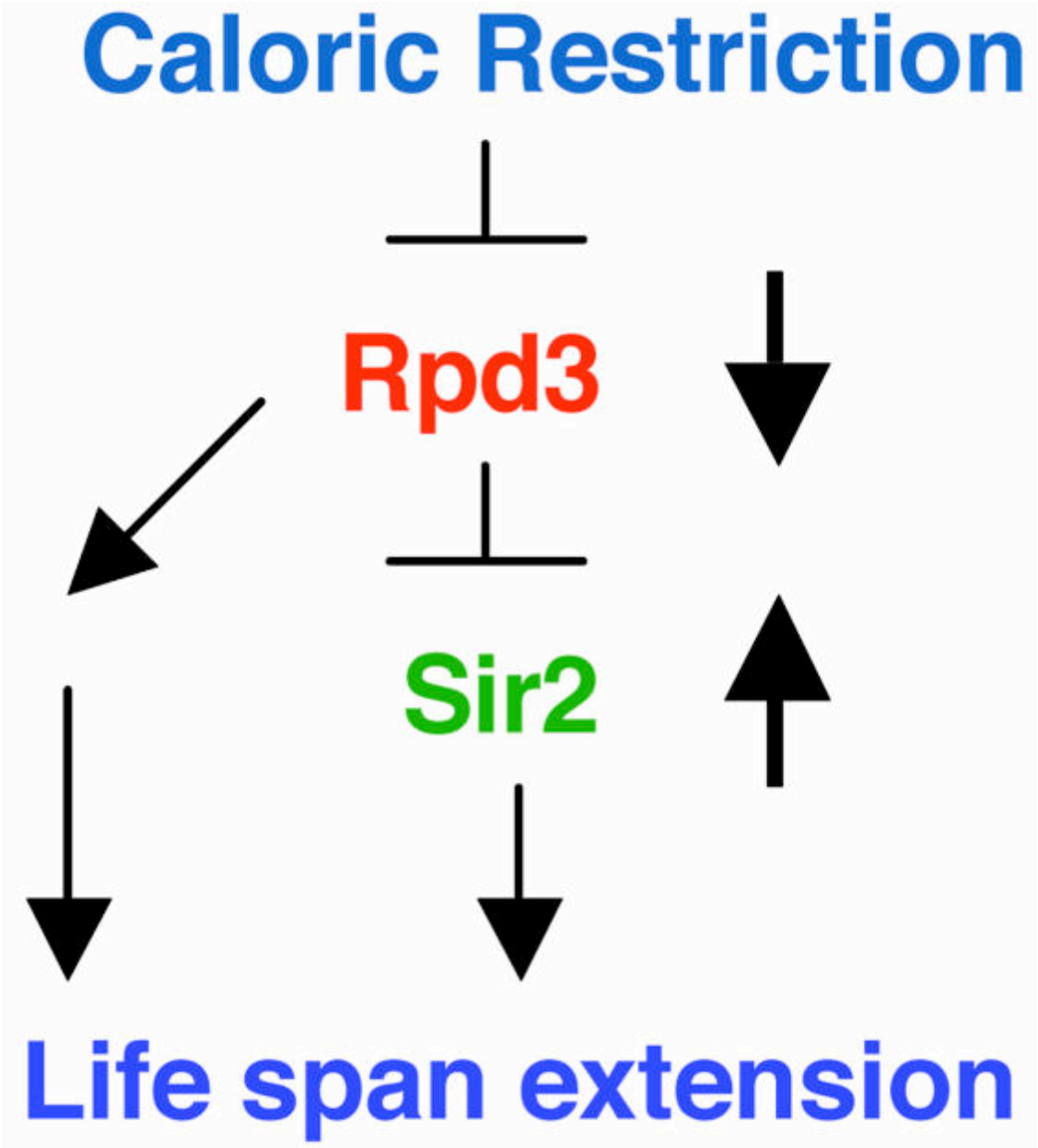
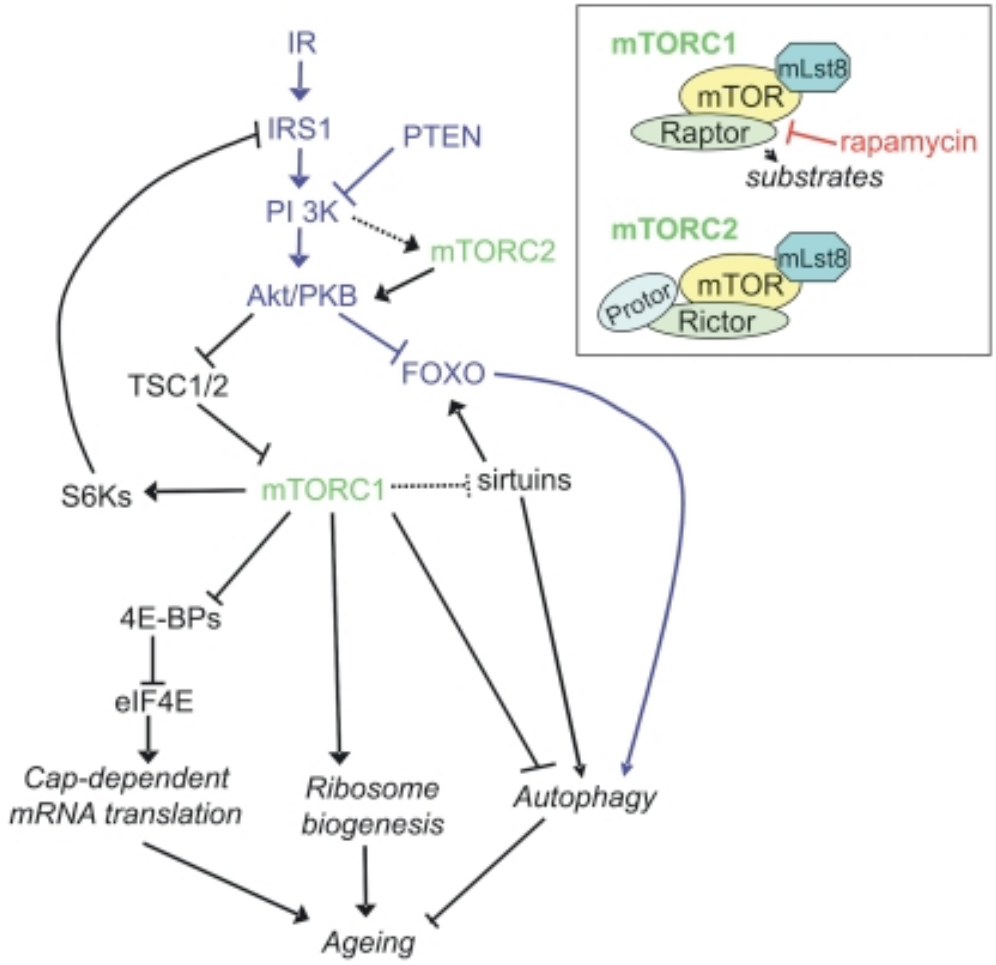

Caloric Restriction
Rpd3
Sir2
Life span extension

TOR (the target of rapamycin)

Protein chinasi coinvolte nella sintesi proteica e nell'autofagia

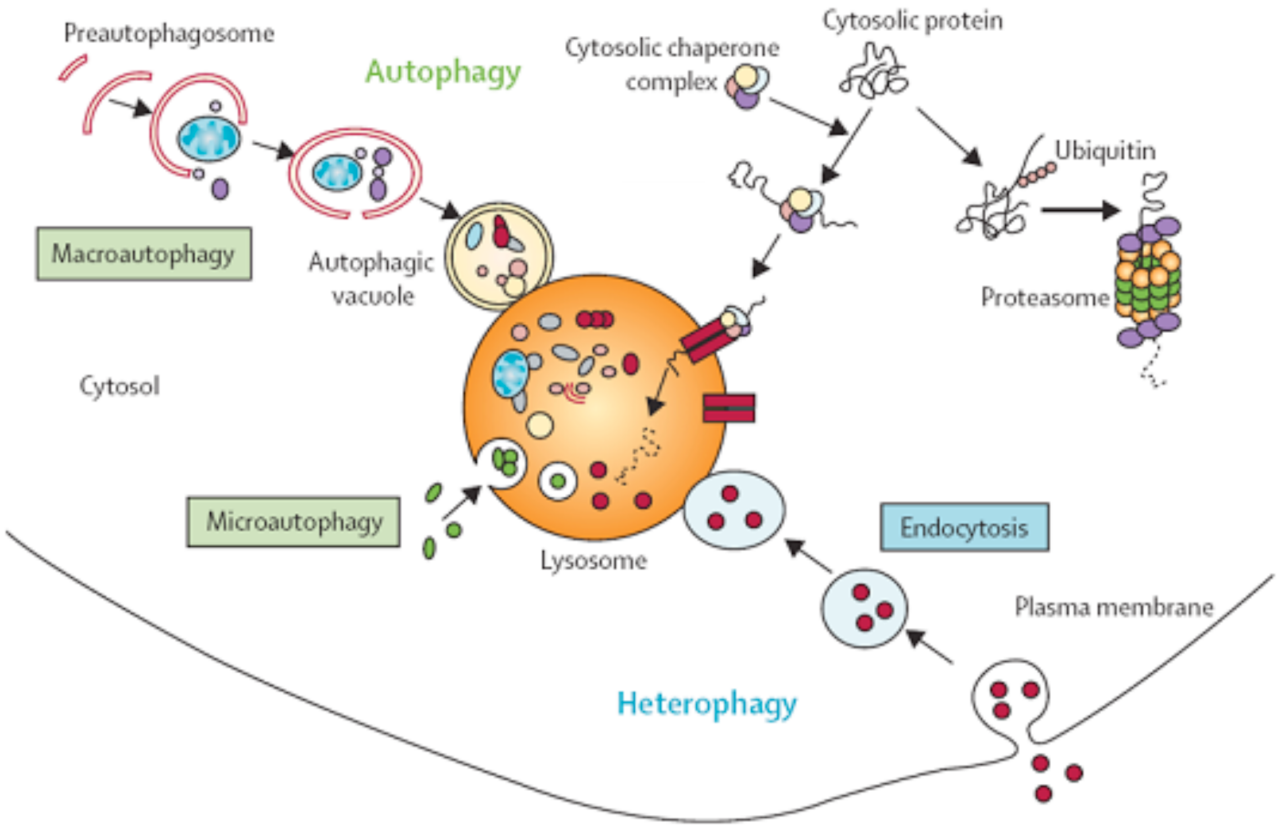
Alterazioni della via di segnalazione TOR estende la durata della vita!

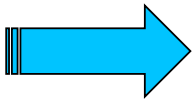
La funzione della via di segnalazione TOR nel controllo dell'invecchiamento suggerisce un legame tra nutrizione, metabolismo e longevità.


IR
IRS1
PTEN
PI 3K
mTORC2
Akt/PKB
TSC1/2
FOXO
S6Ks
mTORC1
sirtuins
4E-BPs
eIF4E
Cap-dependent
mRNA translation
Ribosome
biogenesis
Autophagy
Ageing
mTORC1
mLst8
mTOR
Raptor
rapamycin
substrates
mTORC2
mLst8
Protor
mTOR
Rictor

autofagia

Meccanismo evolutivamente conservato che regola il turnover di componenti citoplasmatici e la rimozione di organelli danneggiati





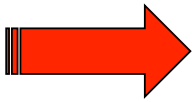


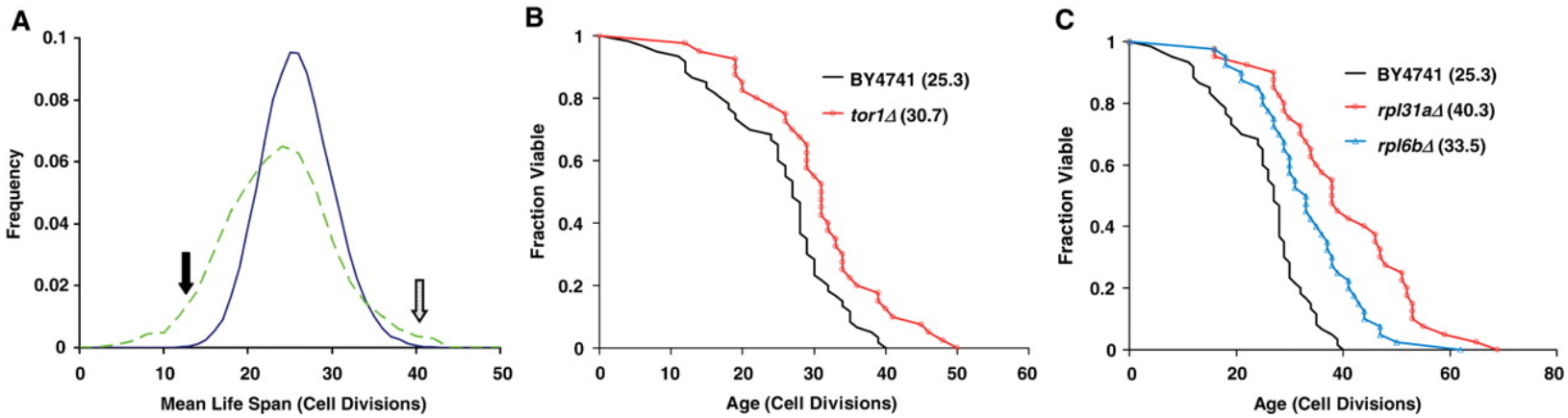
Table 1. List of autophagy and protein synthesis homologs referred to in this review in *S. cerivisiae*, mammals, *C. elegans* and *D. melanogaster* and their effects on lifespan when known

Mammalian	*S. cerivisiae*	*C. elegans*	*D. melanogaster*	Function	Effect on longevity
Unc-51 like kinases 1 & 2 (ULK1&2)	Atg1	Unc-51	DrATG1	Induction of autophagy	Loss of function mutation increases tissue ageing & decreases lifespan in *C. elegans* [49]
APG5	Atg5	Atgr-5	DrATG5	Autophagosome assembly	
Beclin-1	Atg6	Bec-1	DrATG6	Autophagosome assembly	Loss of function mutation increases tissue ageing & decreases longevity in *C. elegans* [49]
APG7	Atg7	Atgr-7	DrATG7	Autophagosome assembly	Knockdown/mutation reduces lifespan in *D. melanogaster* and *C. elegans* [49, 50]
LC3 (APG8)	Atg8	Igg-1	DrATG8	Autophagosome assembly	Reduced expression decreases longevity & enhanced expression increases lifespan in *D. melanogaster* [54,55]
APG12	Atg12	Igg-3	DrATG12	Autophagosome assembly	
WIPI1	Atg18	Atgr-18	CG11975	Recruitment of protein to vesicle membrane	Loss of function mutation increases tissue ageing and decreases lifespan in *C. elegans* [49]
mTOR	TOR	Let-363	DrTOR	Repression of autophagy	Inhibition extends lifespan in yeast, *C. elegans* and *D. melanogaster* [20-22]
S6K	Sch9p	Rsks-1	dS6K	Phosphorylates S6, a component of the 40S ribosomal subunit	Impairing expression in *C. elegans* & *D. melanogaster* extends lifespan [37, 39]
eIF4E	CDC33	Ife-1 – Ife-5	eIF4E-4	Translation initiation (binds mRNA's 5'-cap)	Knockout in *C. elegans* extends lifespan independent of Daf-2 & TOR pathways [39]
Mnk1 and Mnk2	-	Mnk-1	Lk6	eIF4E kinase	Affects lifespan in *D. melanogaster* [43]
FoxA 1, 2 & 3	PHA-4	Pha-4	forkhead	Transcription factor	Enhanced activity increases lifespan [71]
FOXO 1, 3 and 4	-	Daf-16	dFOXO	Transcription factor	Overexpresssion increases lifespan in *D. melanogaster* and *C. elegans*

Regulation of Yeast Replicative Life Span by TOR and Sch9 in Response to Nutrients

Matt Kaeberlein et al.
SCIENCE VOL 310 18 NOVEMBER 2005

Fig. 1. TOR activity is an important modifier of yeast longevity.

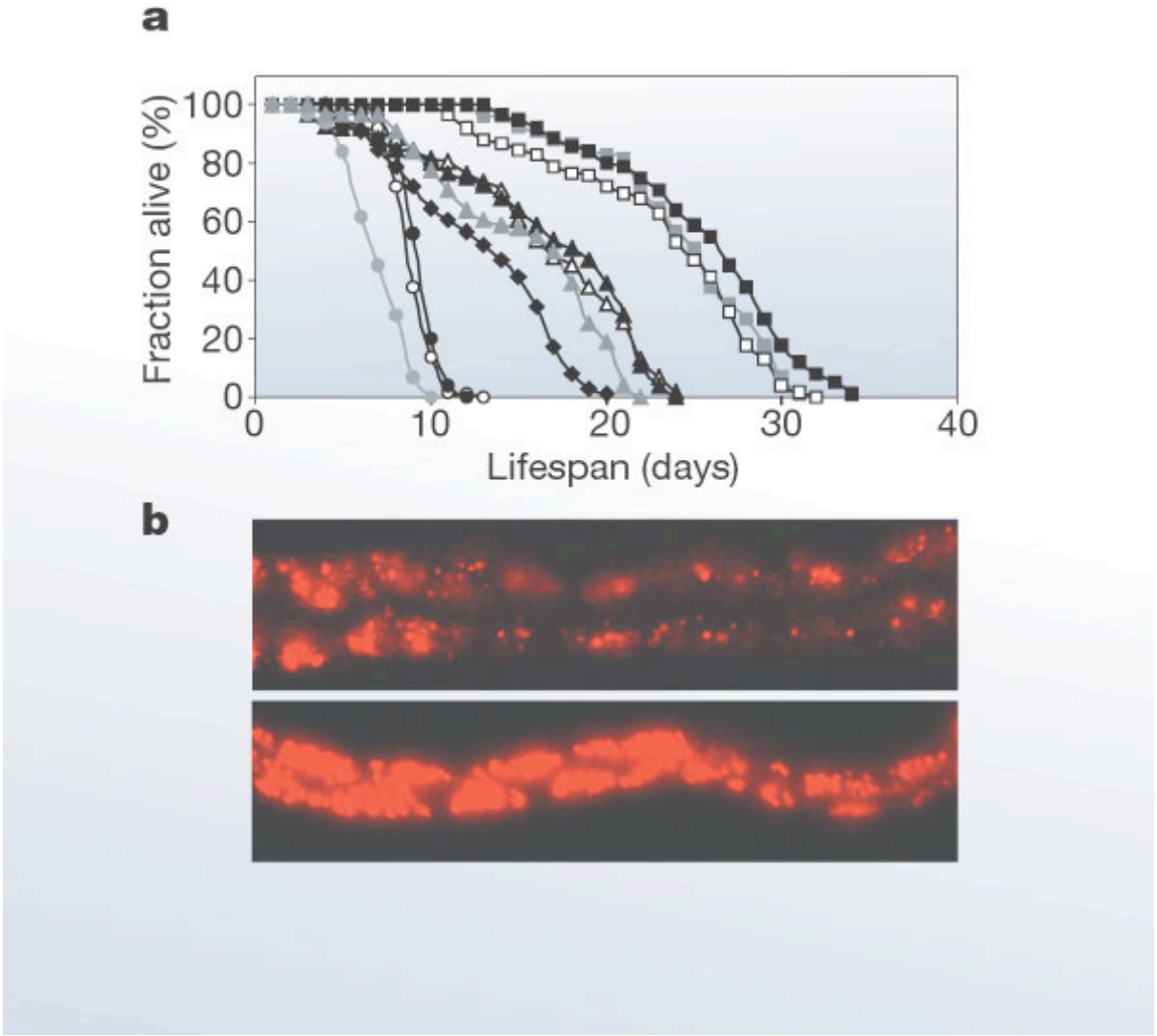


Matt Kaeberlein et al. Science 2005;310:1193-1196

Influence of TOR kinase on lifespan in C. elegans

Tibor Vellai et al.
NATURE|VOL 426 | 11 DECEMBER 2003

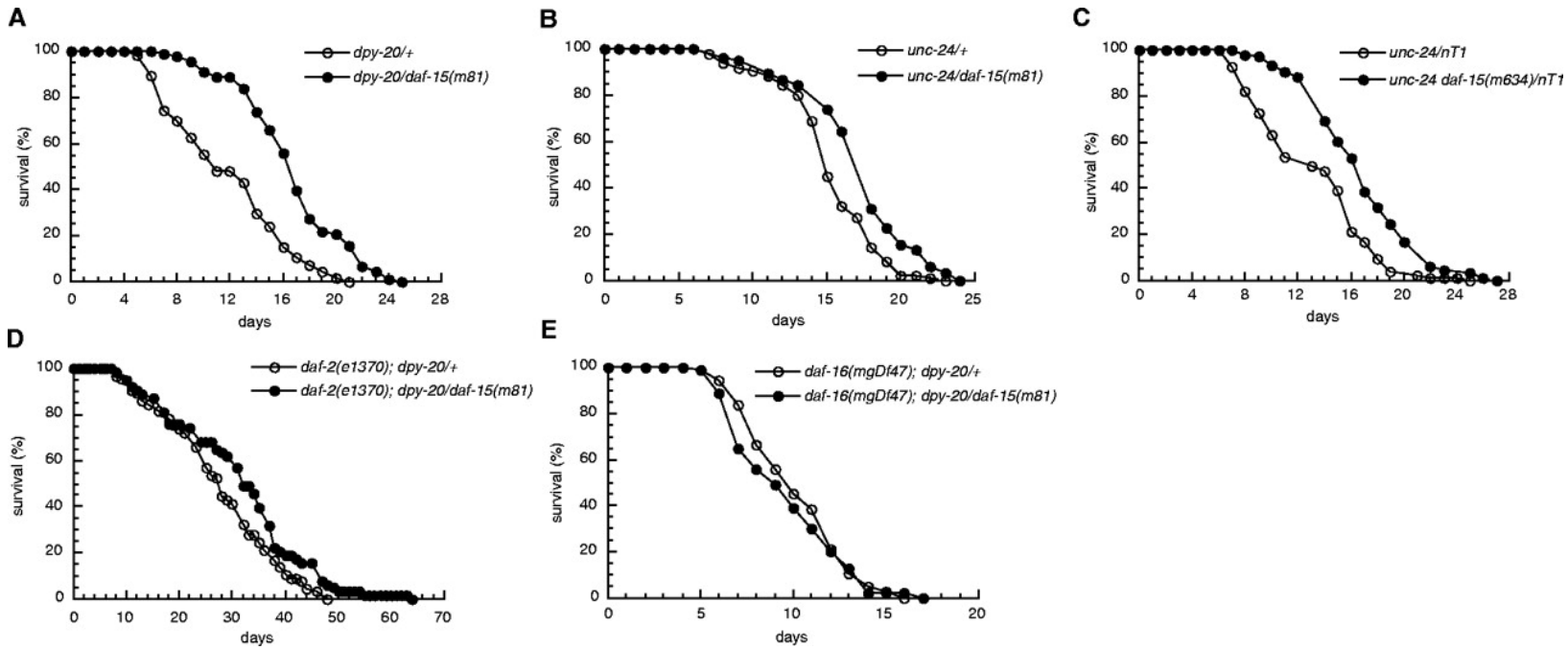
Let-363 mutations extend the lifespan in *C. elegans*



The TOR pathway interacts with the insulin signaling pathway to regulate C. elegans larval development, metabolism and life span

Kailiang Jia, Di Chen and Donald L. Riddle
Development 131, 3897-3906, 2004v

Age phenotype of daf-15/+ mutants in different genetic backgrounds.



Kailiang Jia et al. Development 2004;131:3897-3906

Daf-15 è epistatico su daf-16

WT
daf-2

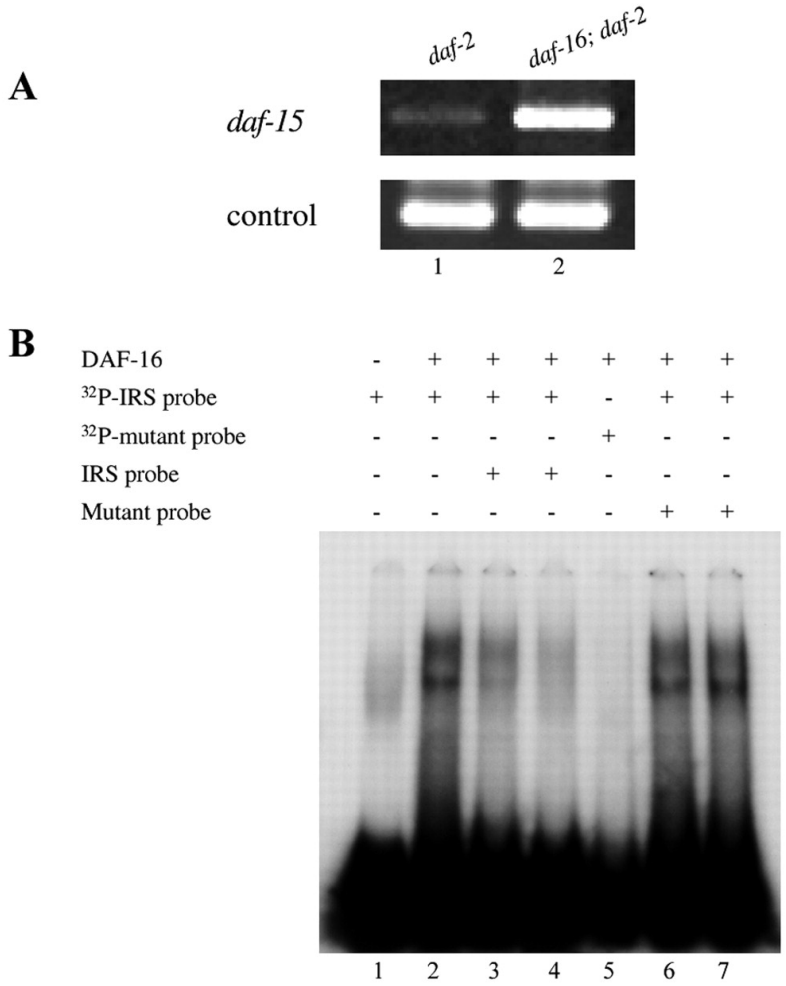
daf-15

let-363

daf-16

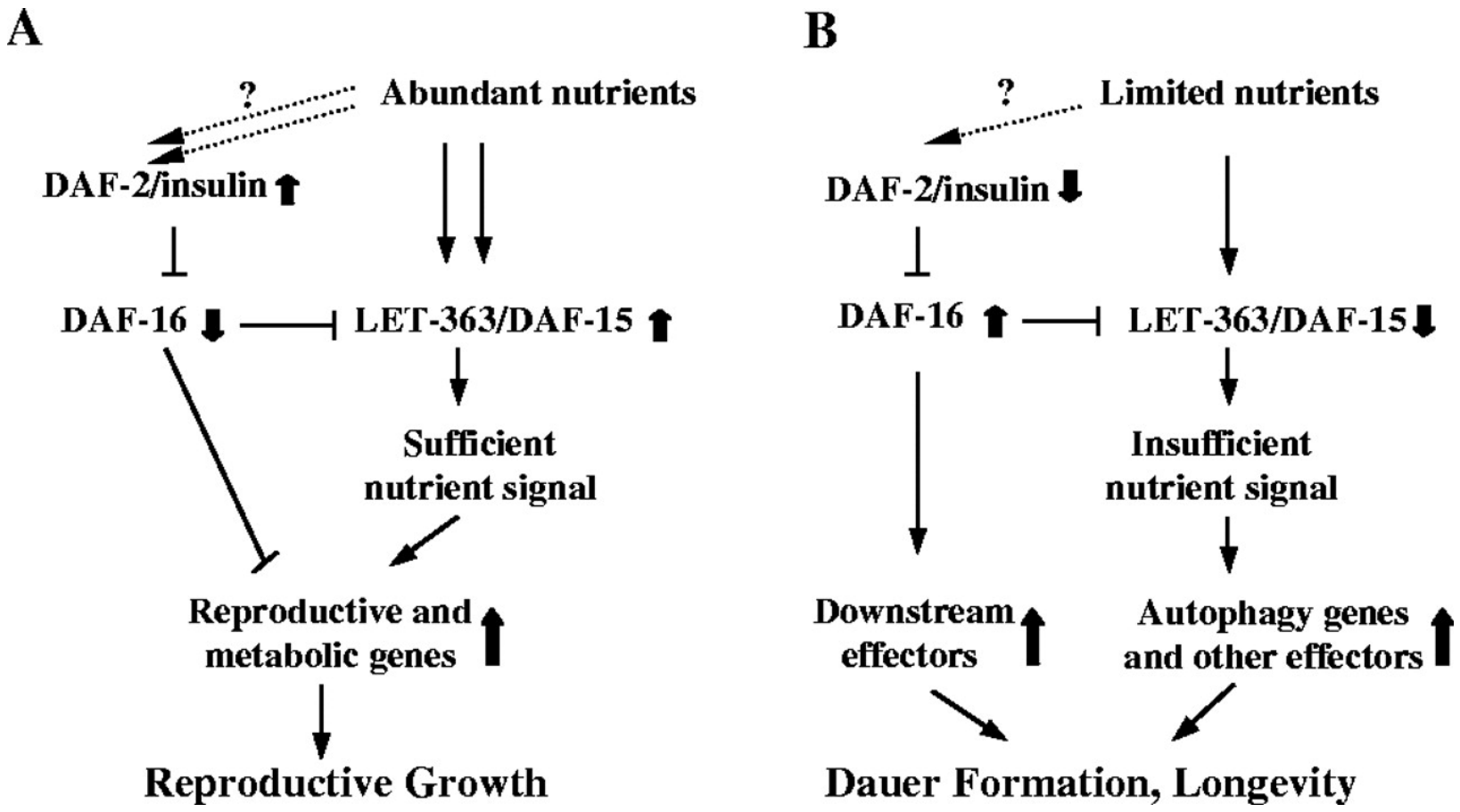
daf-16/daf.15

DAF-16 negatively regulates the expression of daf-15.



Kailiang Jia et al. Development 2004;131:3897-3906

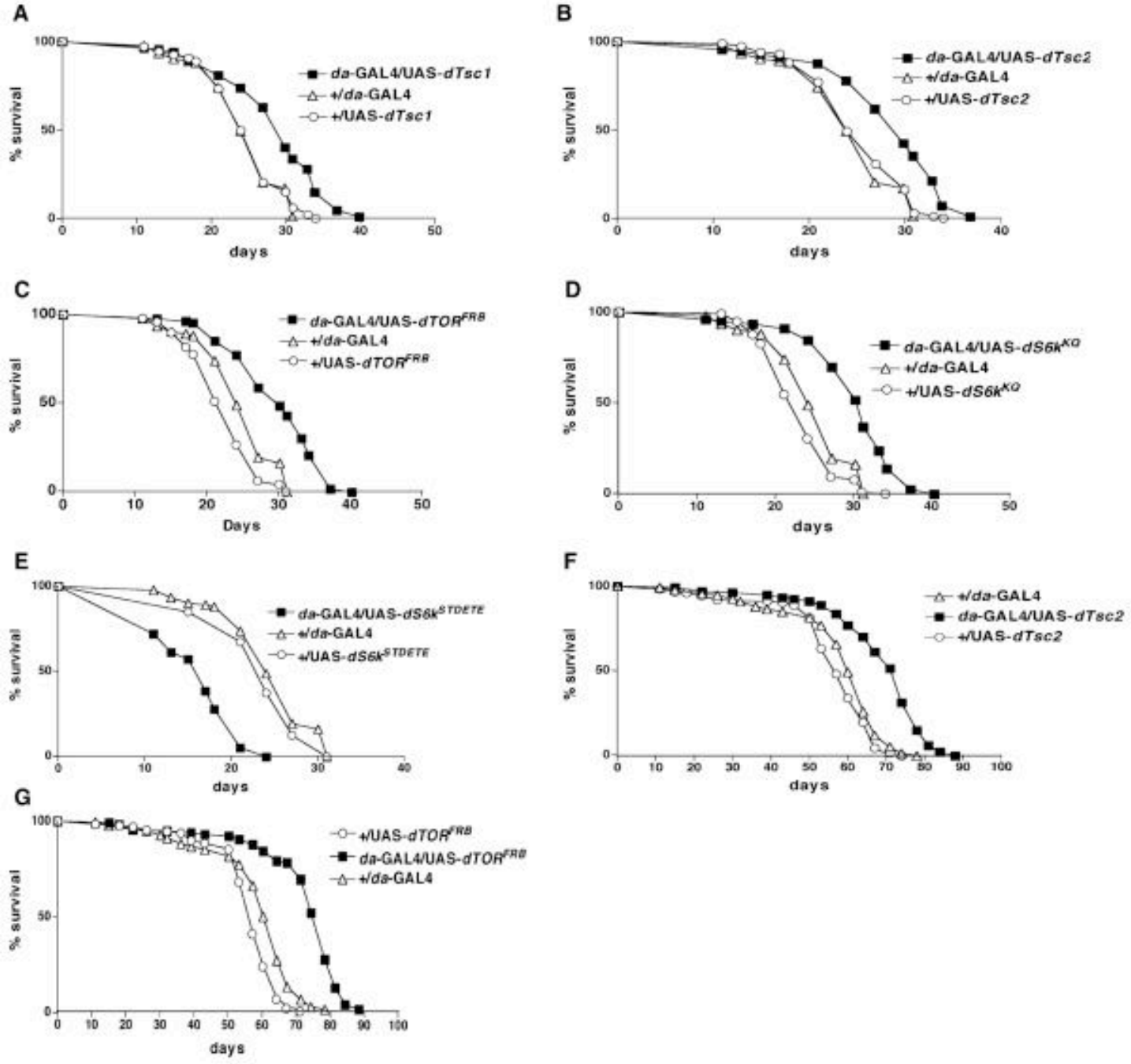
A model for regulation of C. elegans larval development, metabolism and longevity.



Kailiang Jia et al. Development 2004;131:3897-3906

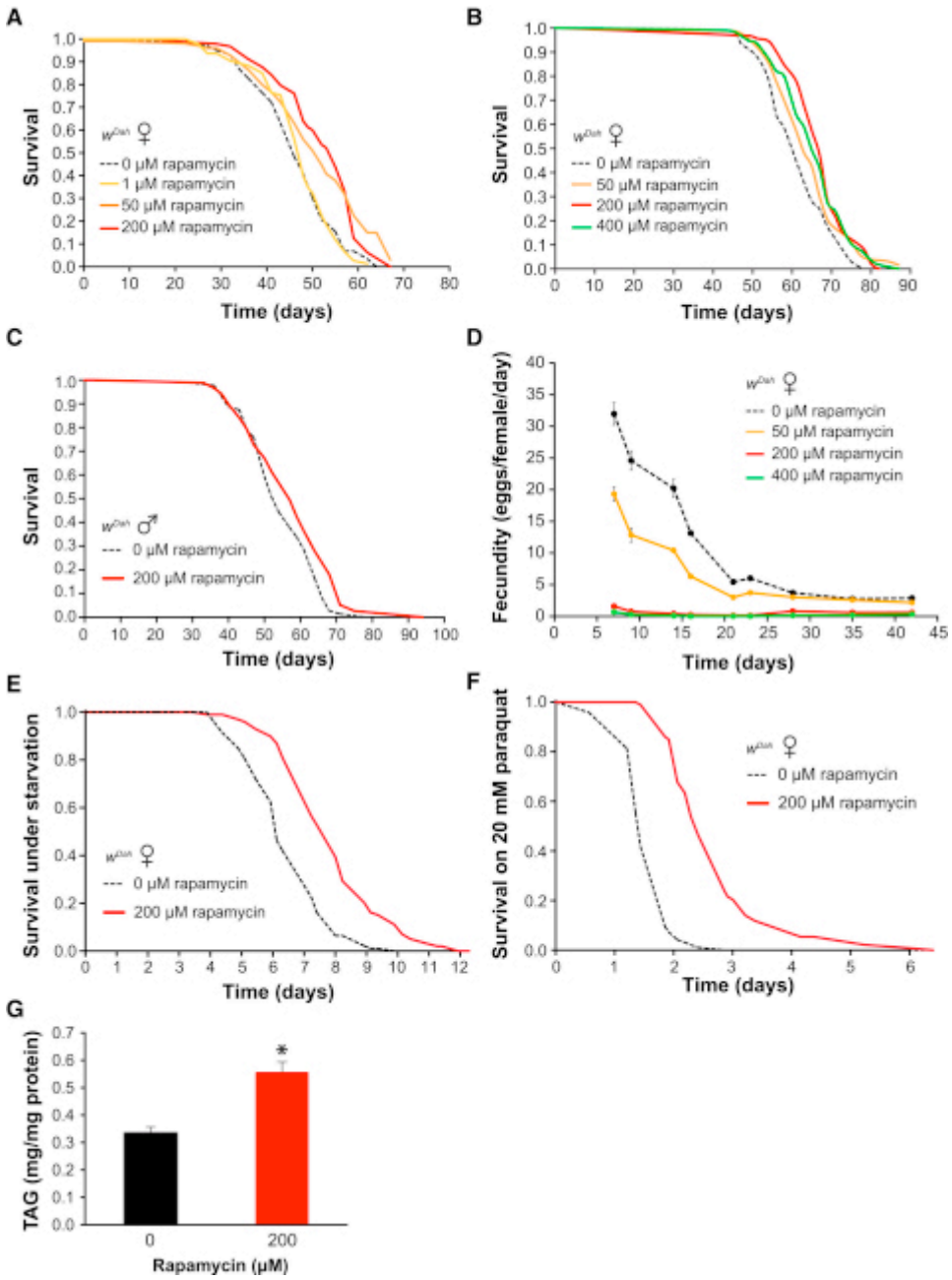
Regulation of Lifespan in *Drosophila* by Modulation of Genes in the TOR Signaling Pathway

Pankaj Kapahi et al.
Current Biology, Vol. 14, 885–890, 2004


A
% survival
days
da-GAL4/UAS-dTsc1
+/da-GAL4
+/UAS-dTsc1
B
% survival
days
da-GAL4/UAS-dTsc2
+/da-GAL4
+/UAS-dTsc2
C
% survival
Days
da-GAL4/UAS-dTOR^FRB
+/da-GAL4
+/UAS-dTOR^FRB
D
% survival
days
da-GAL4/UAS-dS6k^KQ
+/da-GAL4
+/UAS-dS6k^KQ
E
% survival
days
da-GAL4/UAS-dS6k^STDETE
+/da-GAL4
+/UAS-dS6k^STDETE
F
% survival
days
+/da-GAL4
da-GAL4/UAS-dTsc2
+/UAS-dTsc2
G
% survival
days
+/UAS-dTOR^FRB
da-GAL4/UAS-dTOR^FRB
+/da-GAL4

Mechanisms of Life Span Extension by Rapamycin in the Fruit Fly Drosophila melanogaster

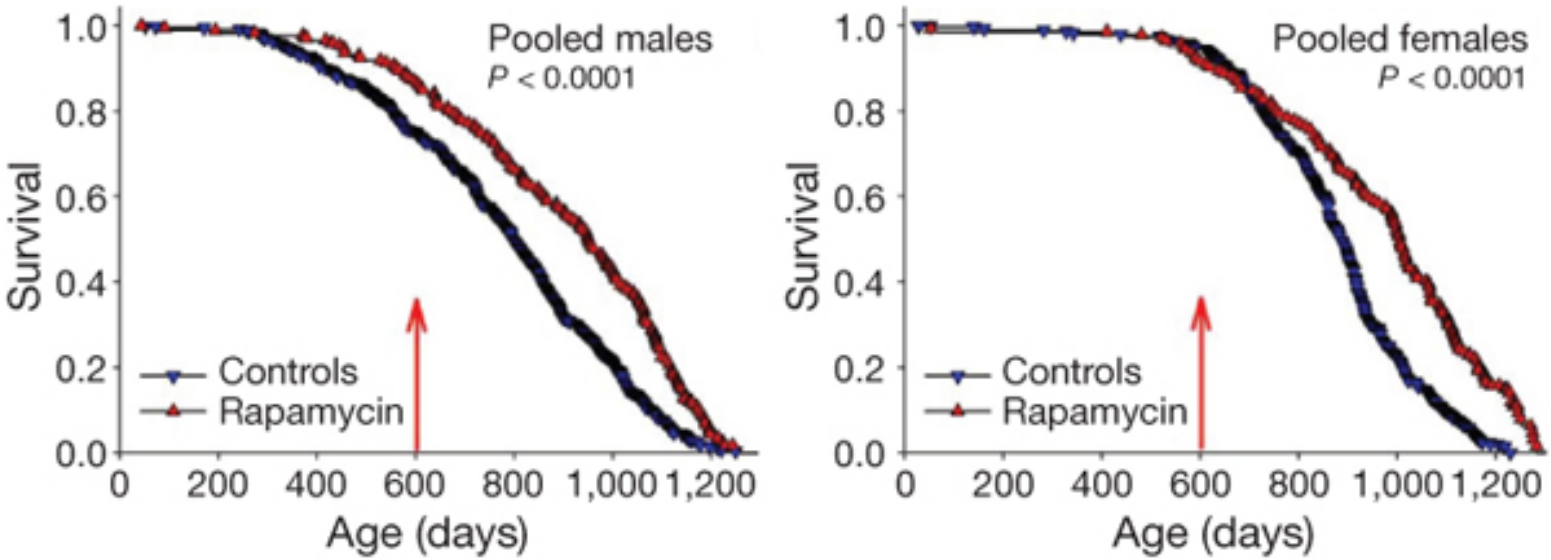
Ivana Bjedov et al. Cell Metabolism 11, 35–46, 2010


A
Survival
Time (days)
w^{Dah} ♀
0 μM rapamycin
1 μM rapamycin
50 μM rapamycin
200 μM rapamycin
B
Survival
Time (days)
w^{Dah} ♀
0 μM rapamycin
50 μM rapamycin
200 μM rapamycin
400 μM rapamycin
C
Survival
Time (days)
w^{Dah} ♂
0 μM rapamycin
200 μM rapamycin
D
Fecundity (eggs/female/day)
Time (days)
w^{Dah} ♀
0 μM rapamycin
50 μM rapamycin
200 μM rapamycin
400 μM rapamycin
E
Survival under starvation
Time (days)
w^{Dah} ♀
0 μM rapamycin
200 μM rapamycin
F
Survival on 20 mM paraquat
Time (days)
w^{Dah} ♀
0 μM rapamycin
200 μM rapamycin
G
TAG (mg/mg protein)
*
0
200
Rapamycin (μM)

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

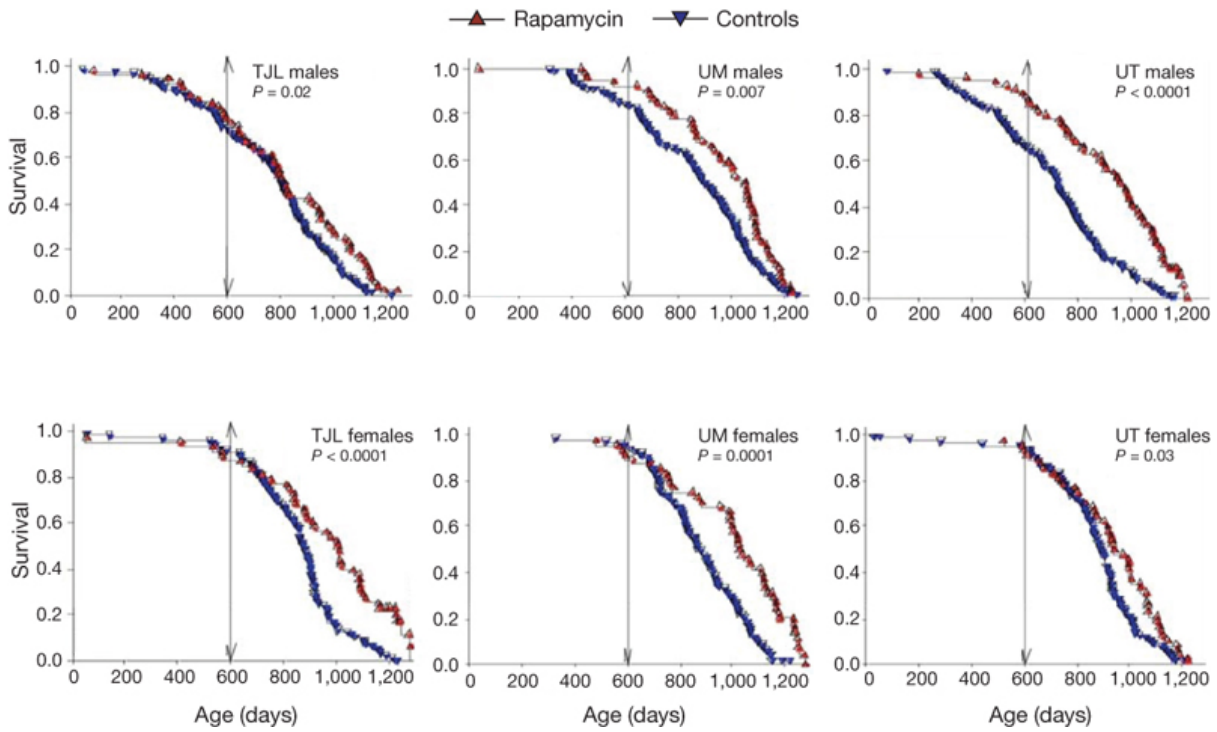
David E. Harrison et al.
NATURE| Vol 460| 16 July 2009

Survival plots for male and female mice, comparing control mice to those fed rapamycin in the diet starting at 600 days of age, pooling across the three test sites.



DE Harrison *et al. Nature* **000**, 1-4 (2009) doi:10.1038/nature08221

Survival of control and rapamycin-treated mice for males and females for each of the three test sites separately.



DE Harrison *et al. Nature* **000**, 1-4 (2009) doi:10.1038/nature08221