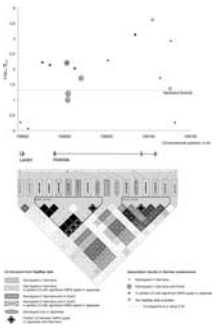
Fine mapping of the FOXO3A region on chromosome 6 (German centenarian sample)

Association of *FOXO3A* variation with human longevity confirmed in German centenarians

The human forkhead box O3A gene (*FOXO3A*) encodes an evolutionarily conserved key regulator of the insulin–IGF1 signaling pathway that is known to influence metabolism and lifespan in model organisms. A recent study described 3 SNPs in the *FOXO3A* gene that were statistically significantly associated with longevity in a discovery sample of long-lived men of Japanese ancestry [Willcox *et al.* (2008) *Proc Natl Acad Sci USA* 105:13987–13992]. However, this finding required replication in an independent population. Here, we have investigated 16 known *FOXO3A* SNPs in an extensive collection of 1,762 German centenarians/nonagenarians and younger controls and **provide evidence that polymorphisms in this gene were indeed associated with the ability to attain exceptional old age.** The *FOXO3A* association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of centenarians for genetic longevity research. **Our study extended the initial finding observed in Japanese men to women and indicates that both genders were likely to be equally affected by variation in *FOXO3A*.** Replication in a French centenarian sample generated a trend that supported the previous results. **Our findings confirmed the initial discovery in the Japanese sample and indicate *FOXO3A* as a susceptibility gene for prolonged survival in humans.**



Flachsbart F. et.al. PNAS 2009;106:2700-2705

PNAS

EVOLUTION OF SENESCENCE

- **Why do organisms age and die?**
- **SENESCENCE – deteriorative changes that occur in an individual with increasing age**

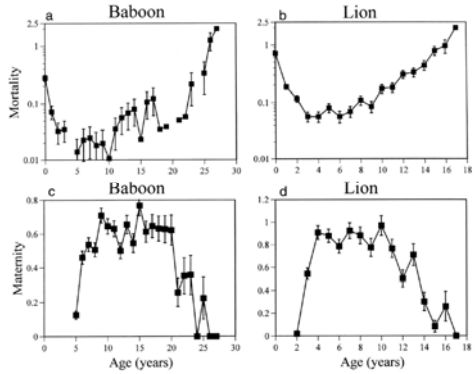
SENESCENCE IS A LIFE HISTORY PHENOMENON

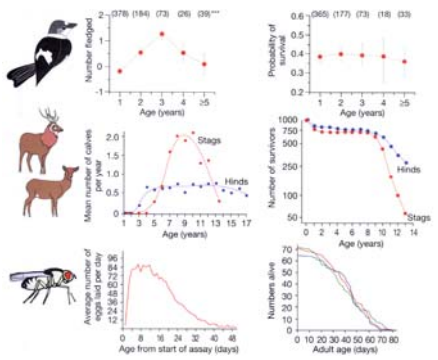
Life History: the stages of growth, reproduction, and dispersal that an individual goes through during its life from birth to death.

SENESCENCE IS A PROPERTY OF POPULATIONS AND SPECIES

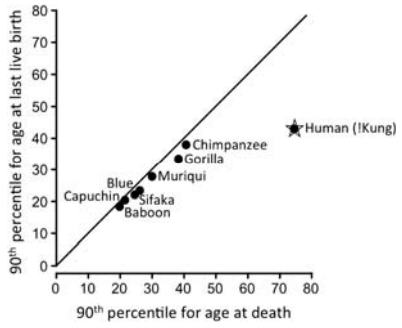
Senescence can be viewed as:

- **A decline in age-specific survival probability**
- **A decline in age-specific reproductive rate**





The life history pacing of fertility completion is different in nonhuman primate species than in humans.



Alberts S C et al. PNAS 2013;110:13440-13445

PNAS

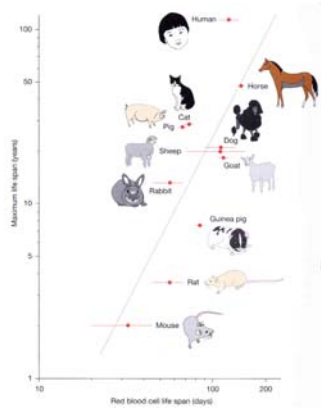
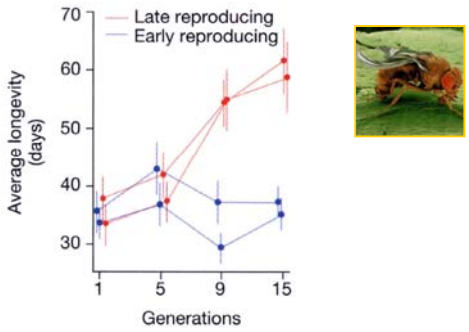


Figure 10.5 The "Y model" for trade-offs between somatic and reproductive function. (Modified from Tatar and Carey 1995 and de Jong and van Nordwijk 1992.)

EVIDENCE OF HERITABLE GENETIC VARIATION FOR LIFESPAN



EVOLUTIONARY EXPLANATIONS FOR SENESCENCE

- **Antagonistic pleiotropy theory**
- **Mutation – Selection Balance theory**

ANTAGONISTIC PLEIOTROPY THEORY

- **Senescence occurs because of the pleiotropic effects of genes.**
- **Selection for alleles which enhance survivorship and/or reproductive rate at early reproductive ages may concomitantly lower survivorship and reproductive rates at later ages.**
- **There is a tradeoff (antagonism) between fitness components early in life and later in life.**

EVIDENCE FOR ANTAGONISTIC PLEIOTROPY

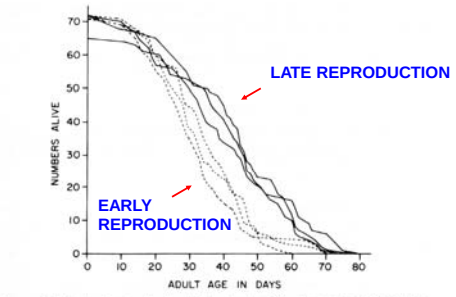


FIGURE 3.7. Survival patterns for females from stocks of *D. melanogaster* maintained using females of different ages. Stocks reproduced using older females are plotted as solid lines. Stocks reproduced using younger females are plotted as dashed lines. (From Rose, 1984b.)

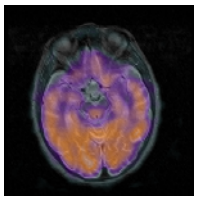
THE INTENSITY OF NATURAL SELECTION DECLINES WITH AGE

…the forces of natural selection *weakens* with increasing age …. If a genetical disaster… happens late enough in individual life, its consequences may be completely unimportant. Even in such a crude and unqualified form, this dispensation may have a real bearing on the origin of innate deterioration with increasing age.

Medawar, 1952

LATE-ONSET MUTATIONS ARE NOT ELIMINATED BY NATURAL SELECTION

EXAMPLE: Huntington's chorea: disabling disorder of the nervous system caused by a dominant mutation that is not expressed until the age of 35 – 40.



George Sumner Huntington

MUTATION-SELECTION BALANCE THEORY

- **Genetic variation is maintained by a balance between the input of variation by mutation at many gene loci and the loss of variation due to selection.**
- **Because selection is weaker at older ages, there is a higher equilibrium level of deleterious mutations with phenotypic effects that are expressed at later ages.**
- **This higher "genetic load" of late-acting deleterious mutations causes senescence.**

HALDANE'S EQUILIBRIUM GENE FREQUENCY

Assume *q* is small, and *u* >> *v* :

- Selection against a completely **recessive** allele:

$W_{AA} = 1$ $W_{Aa} = 1$ $W_{aa} = 1 - s$

$$\hat{q} \cong \sqrt{\frac{u}{s}}$$

- Selection against a completely **dominant** allele:

$W_{AA} = 1$ $W_{Aa} = 1 - s$ $W_{aa} = 1 - s$

$$\hat{q} \cong \frac{u}{s}$$

FUTURE PROSPECTS FOR AGING RESEARCH

People who think they are going to find a fountain of youth, whether at the molecular level or at any level, are not going to be successful.

G. C. Williams

- **Many evolutionary biologists feel that the theories of senescence predict that a medical "fountain of youth" is an unlikely prospect.**
- **Mutation selection balance theory, for example, suggests that late-acting deleterious genes should accumulate at many different loci making the prospect of finding a *single aging gene* impossible.**

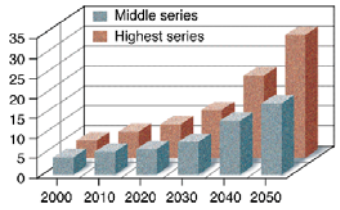
Sardinia's Mysterious Male Methuselahs

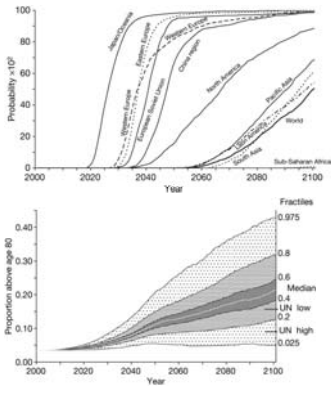
Antonio Todde, age 112

MADAME CALMENT – AGE 122

I don't feel old. I don't feel anything until noon. Then it's time for my nap.
- Bob Hope

DEMOGRAPHIC PROJECTIONS FOR THE PERCENTAGE OF AMERICANS OVER THE AGE OF 65

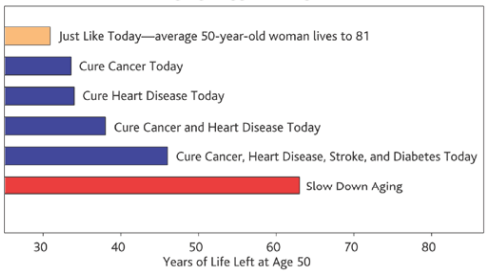




- Probability that populations will reach a proportion of 1/3 of individuals > age 60
- Fraction of Western European populations > 80 years old

Lutz et al. *Nature* 2008

Research on Aging: Biggest Bang for the Buck?



We could certainly slow the aging process down if it had to work its way through Congress. - Will Rogers

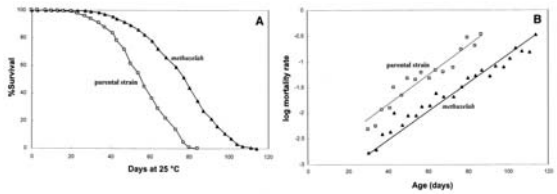
Science: 2003. R.A. Miller/U. of Mich.

"It is clear that directly targeting aging is theoretically superior to treating individual chronic diseases, but until recently, translational approaches to achieve this goal have been just that–purely theoretical."

Healthy aging: The ultimate preventative medicine

SCIENCE sciencemag.org
Matt Kaeberlein,[1]* Peter S. Rabinovitch,[2] George M. Martin[3]*
4 DECEMBER 2015 • VOL 350 ISSUE 6265

EXTENDED LIFE-SPAN AND STRESS RESISTANCE IN THE *DROSOPHILA* MUTANT *METHUSELAH*



Lin et al., Science 1998

WERNER'S SYNDROME

Figure 1. Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image Credit: William and Wilkens Inc.]

Werner's syndrome (WS) is a rare, autosomal recessive disease. Its symptoms are:

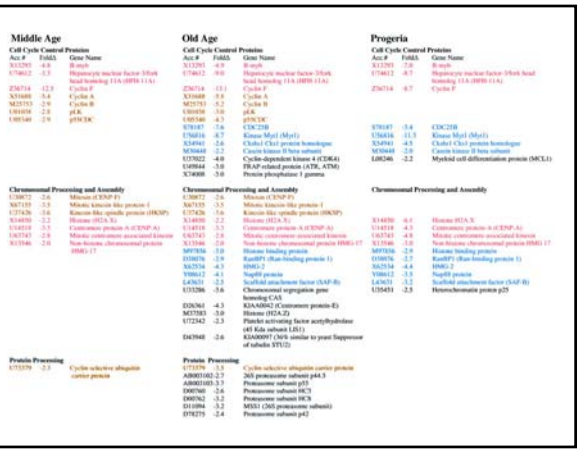
- Growth is deficient post-puberty
- Predisposition to arteriosclerosis, diabetes, non-epithelial cancers
- Premature ageing - wizened appearance, graying hair, hair loss

Cultured cells from patients show:

- Poor division
- Telomere shortening
- Karyotype changes
- Increased mutation rate

The gene was mapped in Japanese families by looking for regions of the genome that were homozygous in patients (because it is a recessive disease). The gene was isolated in 1996. It codes for a **DNA helicase** enzyme.

A RELATED SYNDROME "PROGERIA" MAY LEAD TO INSIGHTS INTO THE PATTERNS OF GENE EXPRESSION RELATED TO HUMAN AGING.



Middle Age

Cell Cycle Control Proteins

Acc #	Fold∆	Gene Name
X13293	-4.0	B-myb
U74612	-3.3	Hepatocyte nuclear factor 3/fork head homolog 11A (HFH-11A)
Z36714	-12.3	Cyclin F
X51688	-5.4	Cyclin A
M25753	-2.9	Cyclin B
U01058	-2.0	pLK
U05340	-2.9	p55CDC

Chromosomal Processing and Assembly

U30872	-2.6	Mitosin (CENP-F)
X67155	-5.0	Mitotic kinesin-like protein-1
U37426	-3.6	Kinesin-like spindle protein (HKSP)
X14850	-2.2	Histone (H2A.X)
U14518	-3.3	Centromere protein-A (CENP-A)
U63743	-2.8	Mitotic centromere-associated kinesin
X13546	-2.0	Non-histone chromosomal protein HMG-17

Protein Processing

U75379	-2.3	Cyclin selective ubiquitin carrier protein

Old Age

Cell Cycle Control Proteins

Acc #	Fold∆	Gene Name
X13293	-4.9	B-myb
U74612	-9.0	Hepatocyte nuclear factor 3/fork head homolog 11A (HFH-11A)
Z36714	-13.1	Cyclin F
X51688	-5.8	Cyclin A
M25753	-5.2	Cyclin B
U01058	-3.0	pLK
U05340	-4.3	p55CDC
S78187	-3.6	CDC25B
U76616	-8.7	Kinase Myt1 (Myt1)
X54941	-2.6	Chdo1 Ckx1 protein homologue
M30448	-2.2	Casein kinase II beta subunit
U37022	-4.0	Cyclin-dependent kinase 4 (CDK4)
U49844	-5.0	FRAP-related protein (ATR, ATM)
X74008	-3.0	Protein phosphatase 1 gamma

Chromosomal Processing and Assembly

U30872	-2.6	Mitosin (CENP-F)
X67155	-3.5	Mitotic kinesin-like protein-1
U37426	-3.6	Kinesin-like spindle protein (HKSP)
X14850	-2.2	Histone (H2A.X)
U14518	-3.3	Centromere protein-A (CENP-A)
U63743	-2.8	Mitotic centromere-associated kinesin
X13546	-2.0	Non-histone chromosomal protein HMG-17
M97856	-5.0	Histone binding protein
D38076	-2.9	RanBP1 (Ran-binding protein 1)
X62534	-4.3	HMG-2
Y08612	-4.1	Nup88 protein
L43631	-2.5	Scaffold attachment factor (SAF-B)
U53286	-3.6	Chromosomal segregation gene homolog CAS
D26361	-4.3	KIAA0042 (Centromere protein-E)
M37583	-3.0	Histone (H2A.Z)
U72342	-2.3	Platelet-activating factor acetylhydrolase (45 Kda subunit LIS1)
D42940	-2.6	KIAA0097 (36% similar to yeast Suppressor of tubulin STU2)

Protein Processing

U75379	-2.3	Cyclin selective ubiquitin carrier protein
AB003102	-2.7	26S proteasome subunit p44.5
AB003103	-3.3	Proteasome subunit p53
D00760	-2.6	Proteasome subunit HC7
D00762	-3.2	Proteasome subunit HC8
D11094	-3.2	MSS1 (26S proteasome subunit)
D78275	-2.4	Proteasome subunit p42

Progeria

Cell Cycle Control Proteins

Acc #	Fold∆	Gene Name
X13293	-7.0	B-myb
U74612	-8.7	Hepatocyte nuclear factor 3/fork head homolog 11A (HFH-11A)
Z36714	-8.7	Cyclin F
S78187	-3.4	CDC25B
U76616	-11.3	Kinase Myt1 (Myt1)
X54941	-4.5	Chdo1 Ckx1 protein homologue
M30448	-2.0	Casein kinase II beta subunit
L08246	-2.2	Myeloid cell differentiation protein (MCL1)

Chromosomal Processing and Assembly

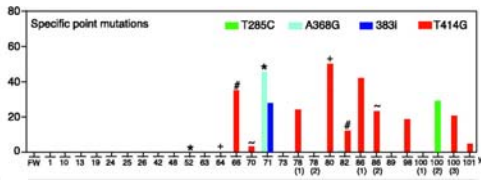
X14850	-6.1	Histone (H2A.X)
U14518	-4.3	Centromere protein-A (CENP-A)
U63743	-4.8	Mitotic centromere-associated kinesin
X13546	-3.0	Non-histone chromosomal protein HMG-17
M97856	-2.9	Histone binding protein
D38076	-2.7	RanBP1 (Ran-binding protein 1)
X62534	-4.4	HMG-2
Y08612	-3.5	Nup88 protein
L43631	-3.2	Scaffold attachment factor (SAF-B)
U35451	-2.5	Heterochromatin protein p25

ACCUMULATION OF MUTATIONS IN THE MITOCHONDRIAL GENOME

Mitochondrial DNA:

- **Mutation rates in mtDNA are 10-20 times that of nuclear genes.**
- **Mitochondria are extremely metabolically active and are an O_2 rich environment.**
- **Leads to free radical damage. Deletion mutations in humans have been shown to increase with age.**

Aging-Dependent Large Accumulation of Point Mutations in the Human mtDNA Control Region for Replication

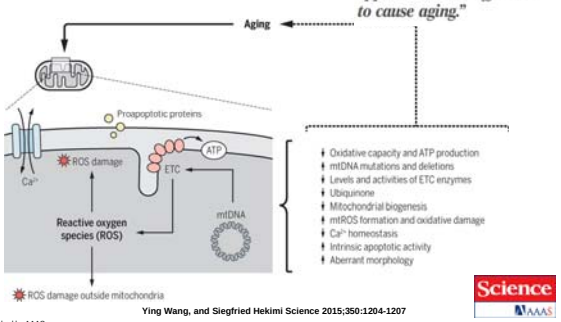


AGE CLASS

FROM: Michikawa Science 1999

Mitochondrial dysfunction and longevity in animals: Untangling the knot

"There is no doubt that mitochondria wear down with age. However, by itself, this functional decline appears to be insufficient to cause aging."

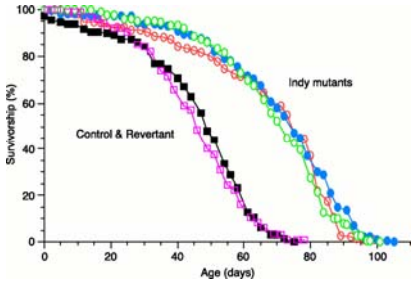


Science AAAS

Ying Wang, and Siegfried Hekimi Science 2015;350:1204-1207

Published by AAAS

CONTROL OF AGING BY THE INDY (I'M NOT DEAD YET) LOCUS



From: Rogina et al. *Science* 290:2137.

Long-lived *Indy* induces reduced mitochondrial reactive oxygen species production and oxidative damage

Nicola Neretti[a,b,1], Pei-Yu Wang[c,1], Alexander S. Brodsky[a], Hieu H. Nyguyen[a], Kevin P. White[c], Blanka Rogina[d,2], and Stephen L. Helfand[b,2]

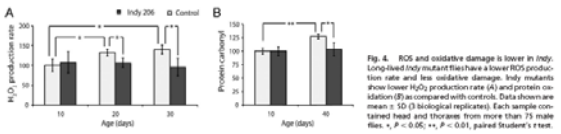
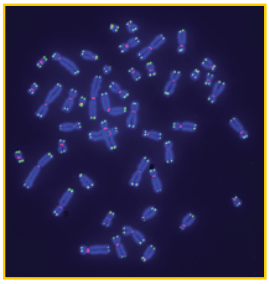
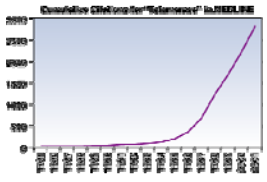


Fig. 4. ROS and oxidative damage is lower in *Indy*. Long-lived Indy mutant flies have a lower ROS production rate and less oxidative damage. Indy mutants show lower H_2O_2 production rate (A) and protein oxidation (B) as compared with controls. Data shown are mean ± SD (3 biological replicates). Each sample contained head and thoraxes from more than 75 male flies. *, $P < 0.05$; **, $P < 0.01$, paired Student's *t* test.

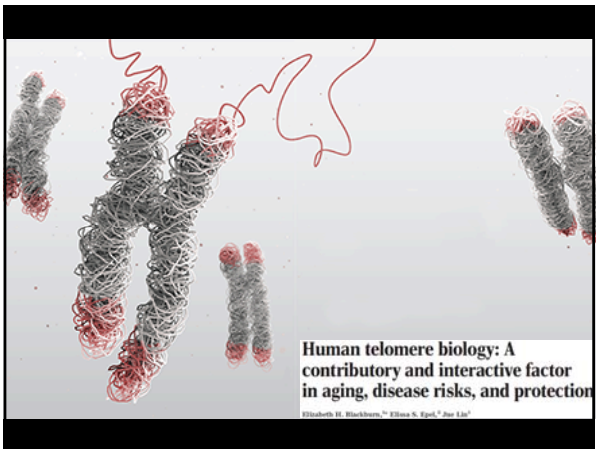
www.pnas.orgcgidoi10.1073pnas.0812484106 PNAS Early Edition 2009



TELOMERASE RESEARCH IS A HOT TOPIC IN AGING AND CANCER RESEACH

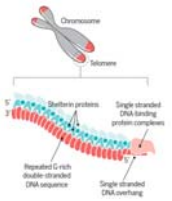


FROM: Marx, 2002. Science 295:2348-2351



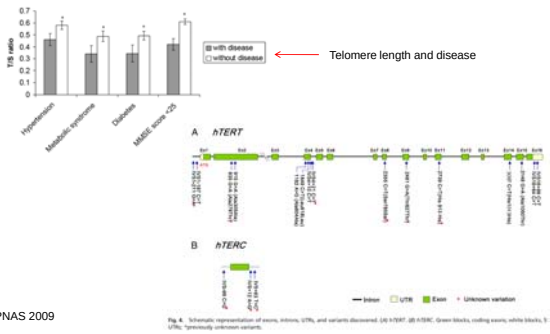
FAILURE OF CELL REPLICATION MAY BE DUE TO DAMAGE TO TELOMERES

- **Telomeres are regions of highly repetitive DNA at the ends of chromosomes.**
- **They prevent the ends of chromosomes from joining together during replication.**
- **DNA polymerases are unable to fully replicate Telomeres.**
- **Telomeres shorten with each cell replication unless they are maintained by telomerase. Eventually the cell is unable to replicate and undergoes "replication senescence".**



Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians

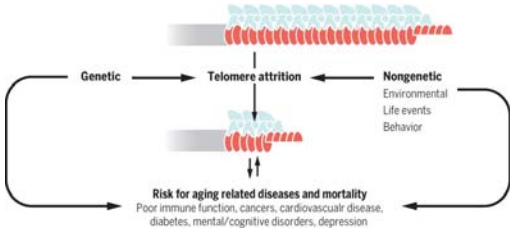
Gil Atzmon[a,b,1,2], Miook Cho[a,1], Richard M. Cawthon[c], Temuri Budagov[b], Micol Katz[b], Xiaoman Yang[b], Glenn Siegel[b], Aviv Bergman[d], Derek M. Huffman[a,b], Clyde B. Schechter[e], Woodring E. Wright[f], Jerry W. Shay[f], Nir Barzilai[a,b], Diddahally R. Govindaraju[g], and Yousin Suh[a,b,2]



Telomere length and disease

PNAS 2009

Relationship of telomere attrition to human aging-related diseases.



Relationship of telomere attrition to human aging-related diseases. Telomere attrition is depicted as an underlying, shared, interactive contributor to the etiologies of aging and aging-related diseases. Because both nongenetic and genetic influences affect it, telomere maintenance is a malleable and integrative indicator of overall health.

Science AAAS

Published by AAAS

Elizabeth H. Blackburn et al. Science 2015;350:1193-1198

"STARVATION" CAN ALSO CHANGE LIFE SPAN

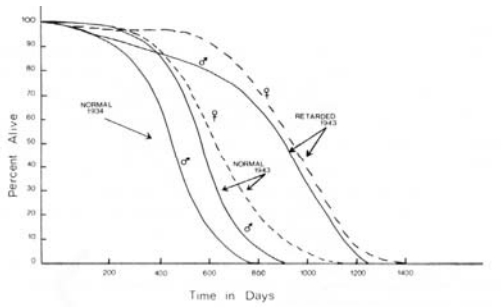
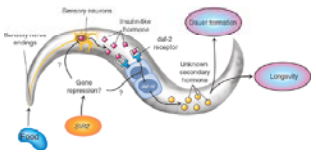


FIGURE 2.10. Survival patterns of "normal" rats, fed ad libitum, and "retarded" rats, which were subjected to nutritional restriction that delayed reproductive maturation. Retarded rats live significantly longer. (From McCay, Sperling, and Barnes, 1943.)

WORKING OUT THE "STARVATION " PATHWAYS

C. elegans & Drosophila



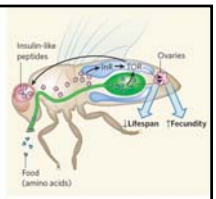


Figure 1 | Signalling pathways possibly influenced by dietary amino acids in *Drosophila*. Grandison *et al.*[3] show that the lifespan-increasing and fecundity-reducing effects of dietary restriction can be attributed to amino-acid limitation. During full feeding, amino acids tend to shorten lifespan and promote egg production. These effects seem to operate via insulin-like signalling, mediated by insulin-like peptides produced in the brain, as mutant flies lacking insulin receptors are protected against the lifespan shortening and loss of fecundity that usually accompany full feeding. During development and growth, insulin signalling interacts with the nutrient-sensing TOR pathway. Because TOR signalling has been implicated in dietary restriction[4,5], insulin/TOR crosstalk could integrate the effects of dietary amino acids on lifespan and reproduction. Blue, fat body; green, digestive system; InR, insulin-like receptor; TOR, target of rapamycin.

Nature (2011) **Published online** 19 October 2011

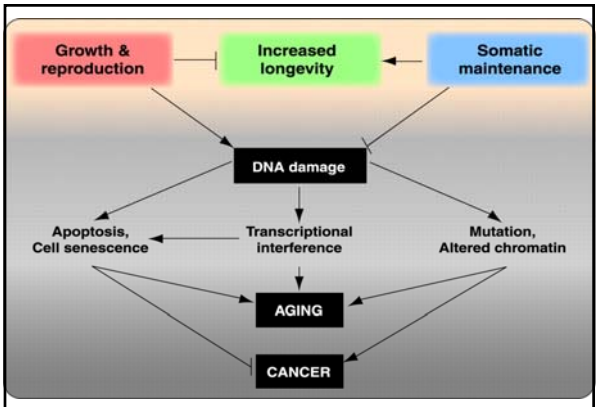
ARTICLE

doi:10.1038/nature10572

Transgenerational epigenetic inheritance of longevity in *Caenorhabditis elegans*

Eric L. Greer[1,2], Travis J. Maures[1], Duygu Ucar[1], Anna G. Hauswirth[1], Elena Mancini[1], Jana P. Lim[1], Bérénice A. Benayoun[1], Yang Shi[2] & Anne Brunet[1]

Chromatin modifiers regulate lifespan in several organisms, raising the question of whether changes in chromatin states in the parental generation could be incompletely reprogrammed in the next generation and thereby affect the lifespan of descendants. The histone H3 lysine 4 trimethylation (H3K4me3) complex, composed of ASH-2, WDR-5 and the histone methyltransferase SET-2, regulates *Caenorhabditis elegans* lifespan. Here we show that deficiencies in the H3K4me3 chromatin modifiers ASH-2, WDR-5 or SET-2 in the parental generation extend the lifespan of descendants up until the third generation. The transgenerational inheritance of lifespan extension by members of the ASH-2 complex is dependent on the H3K4me3 demethylase RBR-2, and requires the presence of a functioning germline in the descendants. Transgenerational inheritance of lifespan is specific for the H3K4me3 methylation complex and is associated with epigenetic changes in gene expression. Thus, manipulation of specific chromatin modifiers only in parents can induce an epigenetic memory of longevity in descendants.



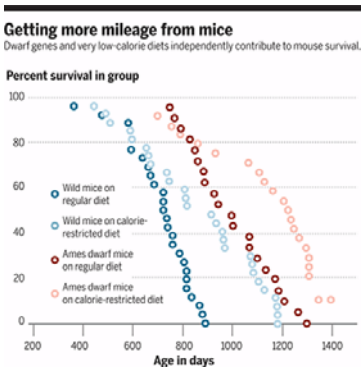
Hasty et al. 2003. Science. 299:1355-1359

This 1463-day-old mouse is part of a long-lived cohort at The Jackson Laboratory.

DEATH-DEFYING EXPERIMENTS

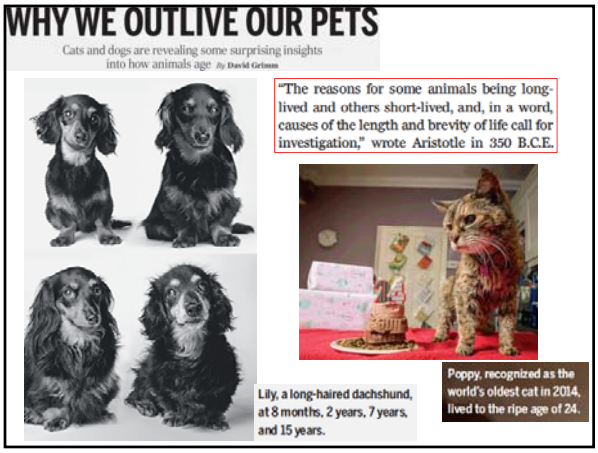
Pushing the limits of life span in animals could someday help lengthen our own

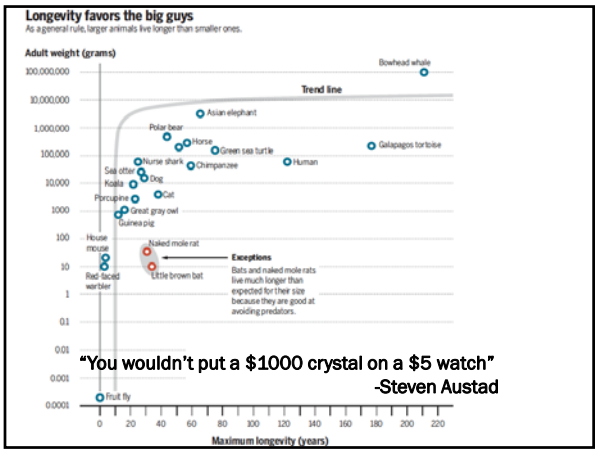
By Jon Cohen



Evolutionary Medicine: From Dwarf Model Systems to Healthy Centenarians?

Longo & Fitch. 2003. Science 299:1342-1346





"You wouldn't put a $1000 crystal on a $5 watch"

-Steven Austad