國立清華大學
National Tsing Hua University

長壽 – 抗老化

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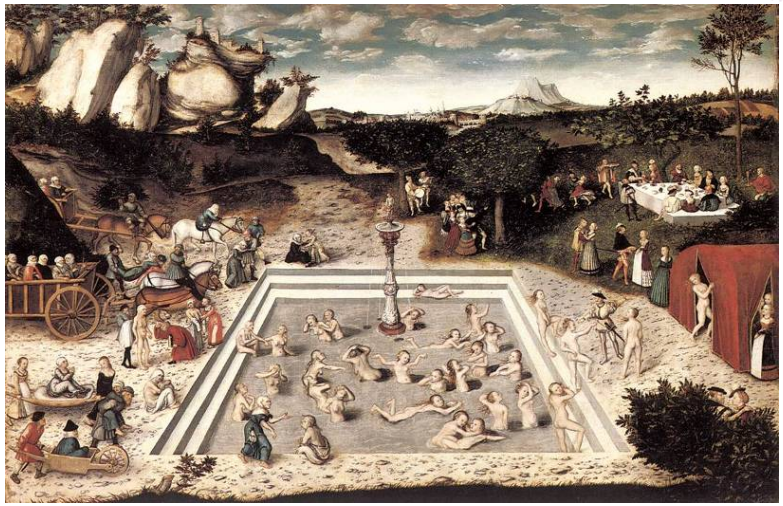
生命科學系暨生物科技研究所

The Fountain of Youth -- Lucas Cranach (1546)

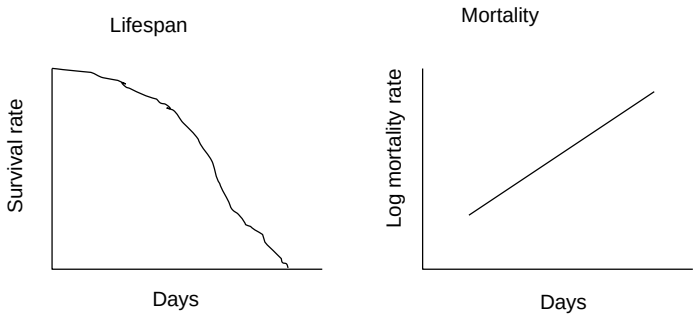


徐福 - 東瀛求仙丹

偷食仙丹 - 常娥奔月宮

What is aging?

Definition: " A time dependent loss of vigor resulting in increased mortality"



Aging theories

Evolutionary: Loss of selection

Mechanistic: Free radical
Caloric restriction
Metabolic rate
Hormone
Replicative senescence

- 細數長壽基因
- 解密長壽基因
- 暫時停止生命
- 尋覓抗老藥丸

細數長壽基因

- 許多基因的功能與生物體的壽命有關，了解這些基因，能使我們的生命後期更健康、更有活力。

- 作者／沈哲鯤

- 「長壽基因」定義爲與壽命長短有關的基因，這些基因在其自然狀態，可能會幫助長壽，也可能抑制壽命的長度。
- 「老化基因」則指與老化有關的基因，它們可能是啓動老化的開始（有無此「開始點」，仍是老化學上未定論之一），也可能是負責（但不一定是專責）調控老化速度。

Aging and longevity genes: strategies for identifying DNA sequences controlling life span.

- 1990年，美國聖安東尼奧德州大學健康科學中心的維琪（Jan Vijg）與德州大學醫學院的帕帕康坦提諾（John Papacontantinou）根據當年一個會議中所發表的報告，以演化學的觀點，於《老人學期刊》發表文章，將與老化有關的基因分爲四類：
- **老化基因**(aging gene):其本身而言，是爲了維持正常的生命進展，而在演化的適應過程中，將生生命帶向終點。
- **傷害性基因**(deleterious gene):則是指在演化的過程中，累積於細胞的某些突變基因，雖然對於早期並無影響，但對於生命後期則有潛在害處。
- **多效基因**(pleiotropic gene):是那些在生命早期具有短暫益處，而在末期卻有不利影響的基因。
- **長壽基因**(longevity gene):則較偏向於指在演化過程中主要執行其他功能，但同時亦會增進存活率與延長壽命的基因。

- 美國密西根大學病理系的米勒（Richard A. Miller）即在2001年一篇論文中，將現今統稱爲長壽基因的基因區分爲六大類:
- 第一類是會導致老化的基因；
- 第二類爲在生命初期較可能使個體不健康，而讓生命長度有所改變的基因，例如致盲基因、小兒糖尿病基因及先天性心臟病基因等；
- 第三類則是決定老年時生活狀況的基因，例如那些導致阿茲海默症、成人型糖尿病、掉髮症的基因；
- 第四種爲低適應性（low fitness）的基因，但卻可能因爲減緩老化的速度而延長了壽命；
- 第五類則是一些基因，由於它們不同對偶基因之間的組合影響了老化，而進一步改變了壽命的長短；
- 第六類則是那些會減緩生物體老化速度的基因。

「長壽基因」的基因有許多

Cross-Species Comparisons of Processes and Genes That Influence Longevity and/or Aging

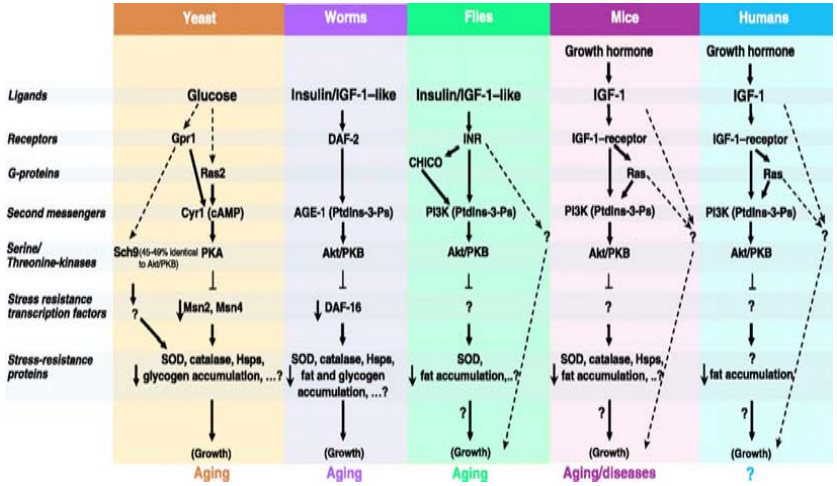
Table 5

	Insulin-Signaling Pathway	Stress Resistance	Metabolic Rate
Nematode	daf-2 age-1 (daf-23)	old-1 old-2 ctl-1 mev-1	clk-1 eat-1 eat-2 sir-2
Fruit fly	InR chico	sod1 mth hsp70 Pcmt	Indy
Mouse	Pit1^{dw} Prop1^{df} Ghrhr^{lit} Ghr Klotho?	Sod2 p66^{shc} MsrA p53?	Upa (caloric restriction?)
Primates (including humans)	PROP1* GHR*	?	Caloric restriction in primates?≠

* Human PROP1 and GHRmutations have been identified,but evidence that they increase life expectancy is fragmentary.
≠ Preliminary results suggest that caloric restriction may extend life expectancy in Rhesus monkeys (Wanagat et al. 1999). Although some mutants have pleiotrophic effects and could be placed in two or more columns,they are listed in the column most relevant to the primary defect.

ILC Workshop Report: ***Longevity Genes: From Primitive Organisms to Humans***

Conserved regulation of longevity in different species



Longo V.D. and Finch C.E. Science *299*, p.1342 (2003)

A systematic RNAi screen for longevity genes in *C. elegans*

Benjamin Hamilton,1 Yuqing Dong,1 Mami Shindo,1 Wenyu Liu,1 Ian Odell,1 Gary Ruvkun,2,3,4 and Siu Sylvia Lee1,3,5

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Genome-wide RNAi screen

Using an RNAi bacterial library targeting >80% of the ~19,000 *C. elegans* open reading frames (Fraser et al. 2000; Kamath et al. 2003) and a high-throughput lifespan assay, we screened for RNAi inactivations that extend the lifespan of wild-type N2 worms. The RNAi clones that were scored positive in the first round of primary screen were subjected to two more rounds of highthroughput lifespan assay. Of the 16,475 RNAi clones tested, ~600 RNAi clones induced lifespan extension above a rather modest threshold in high-throughput screening. Of these ~600 RNAi clones, we performed lifespan assays with many more time points using *rrf- 3(pk1426)*, a mutant with enhanced susceptibility to feeding RNAi (Simmer et al. 2002) and a normal lifespan (Lee et al. 2003a; Murphy et al. 2003). After three rounds of retesting, we identified 90 RNAi clones that significantly extended *C. elegans* lifespan (*P*-value < 0.05) in at least two of the lifespan experiments (Table 1; Supplementary Table 1). The plasmid construct for each of the final 90 RNAi clones was isolated and sequenced to verify its corresponding target gene (Table 1). The 90 RNAi constructs target 89 distinct genes.

GENES & DEVELOPMENT 19:1544–1555, 2005

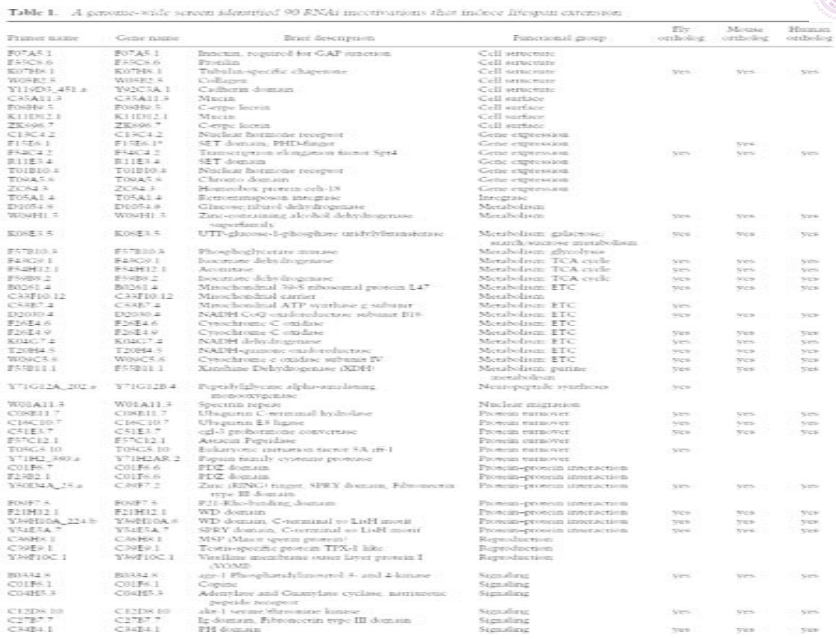


Table 1. *A genome-wide screen identified 90 RNAi inactivations that induce lifespan extension*

Primer name	Gene name	Brief description	Functional group	Fly ortholog	Mouse ortholog	Human ortholog
F07A5.1	F07A5.1	Inactin, required for GAP junction	Cell structure			
F45C8.6	F45C8.6	Protilin	Cell structure			
K07B8.1	K07B8.1	Tubulin-specific chaperone	Cell structure	yes	yes	yes
W08E3.4	W08E3.4	Collagen	Cell structure			
Y41D4B.4.1.a	Y42C5A.1	Calberin domain	Cell structure			
C35A11.8	C35A11.8	Mucin	Cell surface			
F08B8.5	F08B8.5	Cerge lectin	Cell surface			
K11D12.1	K11D12.1	Mucin	Cell surface			
ZK696.7	ZK696.7	Cerge lectin	Cell surface			
C18C4.2	C18C4.2	Nuclear hormone receptor	Gene expression			
F15E6.1*	F15E6.1*	SET domain, PHD-finger	Gene expression		yes	
F44C4.2	F44C4.2	Transcription elongation factor Spt4	Gene expression	yes	yes	yes
B11E3.4	B11E3.4	SET domain	Gene expression			
T01B10.4	T01B10.4	Nuclear hormone receptor	Gene expression			
T04A5.6	T04A5.6	Chromo domain	Gene expression			
ZC84.8	ZC84.8	Homeobox protein cch-1/8	Gene expression			
T05A12.4	T05A12.4	Retroviruspoxin integrase	Integrase			
D1054.9	D1054.9	Glucose/ribitol dehydrogenase	Metabolism			
W04H1.5	W04H1.5	Zinc-containing alcohol dehydrogenase superfamily	Metabolism	yes	yes	yes
K08E3.5	K08E3.5	UTP-glucose-1-phosphate uridylyltransferase	Metabolism: galactose, starch/sucrose metabolism	yes	yes	yes
F57B10.8	F57B10.8	Phosphoglycerate mutase	Metabolism: glycolysis			
F45C9.1	F45C9.1	Isocitrate dehydrogenase	Metabolism: TCA cycle	yes	yes	yes
F42H12.1	F42H12.1	Aconitase	Metabolism: TCA cycle	yes	yes	yes
F56B9.2	F56B9.2	Isocitrate dehydrogenase	Metabolism: TCA cycle	yes	yes	yes
B0261.4	B0261.4	Mitochondrial 39-S ribosomal protein L47	Metabolism: ETC	yes	yes	yes
C39E10.12	C39E10.12	Mitochondrial carrier	Metabolism			
C35E7.4	C35E7.4	Mitochondrial ATP synthase g subunit	Metabolism: ETC	yes		
D2030.4	D2030.4	NADH CoQ oxidoreductase subunit B18	Metabolism: ETC	yes	yes	yes
F26E4.6	F26E4.6	Cytochrome C oxidase	Metabolism: ETC			
F26E4.9	F26E4.9	Cytochrome C oxidase	Metabolism: ETC	yes	yes	yes
K04G7.2	K04G7.2	NADH dehydrogenase	Metabolism: ETC	yes	yes	yes
T20B4.5	T20B4.5	NADH-quinone oxidoreductase	Metabolism: ETC	yes	yes	yes
W09C5.6	W09C5.6	Cytochrome c oxidase subunit IV	Metabolism: ETC	yes	yes	yes
F57B11.1	F57B11.1	Xanthine Dehydrogenase (XDH)	Metabolism: purine metabolism	yes	yes	yes
Y71G12A_2G2.a	Y71G12B.4	Peptidyllysine alpha-oxidizing monooxygenase	Neuropeptide synthesis	yes		
W08A11.3	W08A11.3	Specrin repeat	Nuclear migration			
C39E11.7	C39E11.7	Ubiquitin C-terminal hydrolase	Protein turnover	yes	yes	yes
C39C10.7	C39C10.7	Ubiquitin E2 ligase	Protein turnover	yes	yes	yes
C51E3.7	C51E3.7	spl-3 prolyltetrole conversase	Protein turnover	yes	yes	yes
F57C12.1	F57C12.1	Asparn Peptidase	Protein turnover			
T09C8.10	T09C8.10	Eukaryotic translation factor 5A (eIF-1	Protein turnover	yes		
Y71H2_380.a	Y71H2AB.2	Papain family cysteine protease	Protein turnover			
C01F6.7	C01F6.6	PDZ domain	Protein-protein interaction			
F28D2.1	C01F6.6	PDZ domain	Protein-protein interaction			
Y8DEMA_15.a	C39F7.2	Zinc (RING) finger, SPRY domain, Fibronectin type III domain	Protein-protein interaction	yes	yes	yes
F09F7.6	F09F7.6	F21-Rho-binding domain	Protein-protein interaction			
F21H12.1	F21H12.1	WD domain	Protein-protein interaction	yes	yes	yes
Y39E10A_324.b	Y39E10A.6	WD domain, C-terminal to LisH motif	Protein-protein interaction	yes	yes	yes
Y54E5A.7	Y54E5A.7	SPRY domain, C-terminal to LisH motif	Protein-protein interaction	yes	yes	yes
C34B8.1	C34B8.1	MSP (Major sperm protein)	Reproduction			
C39E9.1	C39E9.1	Testis-specific protein, TPX-1 like	Reproduction			
Y39E10C.1	Y39E10C.1	Vanilloid membrane ionic Level protein 1 (VOM2)	Reproduction			
B0334.8	B0334.8	age-1 Phosphatidylinositol 3- and 4-kinase	Signaling	yes	yes	yes
C01F6.1	C01F6.1	Cyclin	Signaling			
C04H5.9	C04H5.9	Adenylate and Guanylate cyclase, natriuretic peptide receptor	Signaling			
C12D8.10	C12D8.10	akt-1 serine/threonine kinase	Signaling	yes	yes	yes
C27F7.7	C27F7.7	Ig domain, Fibronectin type III domain	Signaling	yes	yes	yes
C34E4.1	C34E4.1	PH domain	Signaling	yes	yes	yes

「長壽基因」的基因有許多

- SIR2即爲其中一個。有趣的是，SIR2及其同類基因族的延壽功能與「低熱量飲食」息息相關，在其他生物中，則會影響許多蛋白質，特別是一些基因轉錄因子及訊息傳遞分子的活性，進而影響許多其他基因的表現以及細胞中DNA修補、細胞保護及新陳代謝等過程；這些過程的品質，則進一步影響壽命長短。

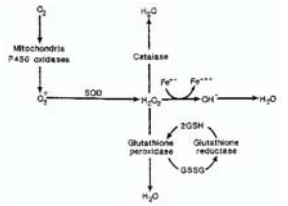
- 除SIR2之外，有許多其他基因，當過量表現時，亦會增加生命長度，這包括了一些熱休克蛋白（heat shock protein）及超氧化物歧化酶（superoxide dismutase）。
- 熱休克蛋白功能多樣，有些是在正常生活中維持蛋白質的完整與協助其他蛋白質到達其所該在的細胞位置；某些則可以阻止因受熱產生的不正常蛋白質聚集現象，並協助受損蛋白質恢復正常的結構；而生物個體在老化的過程當中，對於冷、熱及飢餓等壓力的忍受度較年輕時降低許多，所以如果熱休克蛋白增加，應對老化生物個體中的細胞有幫助。
- 自由基被認爲是老化的元兇之一。在生物個體中具有抗氧化的機制來避免自由基所產生的傷害，而超氧化物歧化酶的作用就是將自由基轉換成無害的物質，以減輕對生物體的損傷；但是這種防禦機能，也會隨著歲月的增長而減退。另外有一些基因，當它們產生突變而減少了經由胰島素或其他類似蛋白的訊息傳遞時，也可使得生物的生命延長。

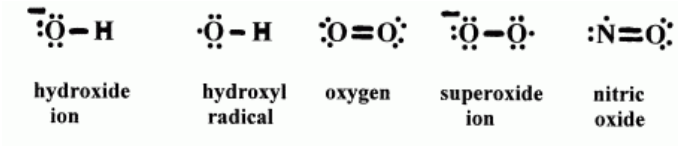
Oxidative Damage

- The free radical theory of aging was first proposed by **Denham Harman** in November, **1954**.

Free radicals *are cellular renegades; they wreak havoc by damaging DNA mitochondria, altering biochemical compounds, corroding cell membranes and killing cells outright. Such molecular mayhem, scientists increasingly believe, plays a major role in the development of ailments like cancer, heart or lung disease and cataracts. Many researchers are convinced that the cumulative effects of free radicals also underlie the gradual deterioration that is the hallmark of aging in all individuals, healthy as well as sick.*

—TIME, April 6, 1992





oxygen free radical molecules

The evidence that oxidative damage causes aging

- Transgenic *Drosophila* overexpressing both Cu/Zn SOD and catalase live 34% longer than controls.
- The expression of human *SOD1* exclusively in *Drosophila* adult motor neurons leads to a 40% extension in life span. (by UAS/GAL4 system, see next slide)

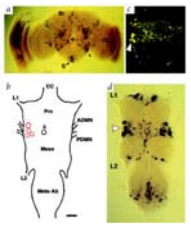


Figure 1. GAL4-activated expression of human *SOD1* in motorneurons.
Whole mounts of adult brain and ventral ganglia hybridized *in situ* with a full length dioxygenin–labelled human SOD1 (HS) cDNA. Tissues were examined from transgenic flies bearing one copy each of HS1 and D42-GAL4 (HS1/+;GAL4/+). **a** , Transgenic HS expression was detected primarily in the central brain (Br), lateral margins adjacent to the lobula/lobula plate (arrowheads), and suboesophageal ganglia (S). No expression was detected in the optic lobes (OL) or retina (R). **b** , A schematic of the ventral ganglia depicting the location of four ganglionic regions: prothoracic (Pro), mesothoracic (Meso), and combined metathoracic and abdominal ganglia (Meta–Ab). Peripheral nerves which act as landmarks are also shown, (ADMN, PDMN; L1 and L2). Four of the five identifiable flight motorneurons (red circles) are ventrally located, the fifth is located dorsally. **c** , The expression of the D42-GAL4 line was determined by immunofluorescence after crossing to flies containing a UAS-GFP transgene. Illustrated is the result of a z-series of confocal images through the ventral ganglia. The location of four of the large flight muscle motorneurons is indicated by an arrowhead. **d** , Expression of HS can be detected within flight muscle motorneurons 1-4 (*) as well as other motorneurons distributed at various locations within the ventral ganglia. Scale bar: *a*, 200 m, *b*, 100 m.

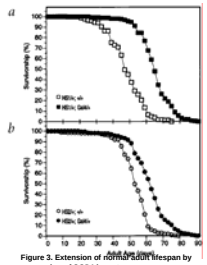


Figure 3. Extension of normal adult lifespan by expression of *SOD1* in motorneurons.
Adult *Sod*$^{+/+}$ males (0-24-h old) bearing a single copy of HS1 (**a**) or HS2 (**b**) and either one or no copies of D42-GAL4 were maintained at 25 °C in shell vials (10 flies per vial) containing standard cornmeal agar medium. The starting population size for each genotype was 250. Flies were transferred to fresh medium and scored for survivorship every two days. The mean (50% mortality) and maximum (90% mortality) lifespan for each genotype is as follows: HS1/+;+/+ (mean = 45.1 3.4; max. = 56.3 3.6); HS1/+;D42GAL4/+ (mean = 63.7 4.3; max. = 73.2 3.4; HS2/+;+/+ (mean = 52.2 1.8; max. = 58.8 1.5); HS2/+;D42GAL4/+ (mean = 60.6 2.2; max. = 71.0 2.7). The lifespan of the D42-GAL4/+;+/+ control is very similar to the HS/+;+/+ strains. Expression of HS under the transcriptional control of other GAL4 drivers, including a heatshock-GAL4 construct which drives expression broadly at all stages of development and an elav-GAL4 construct which drives expression at high levels in embryonic and larval neurons, did not extend lifespan (data not shown).

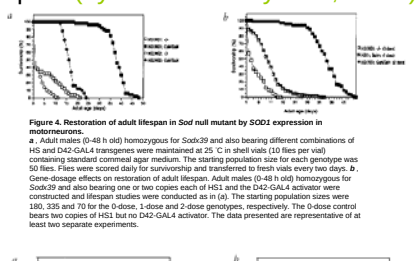


Figure 4. Restoration of adult lifespan in *Sod* null mutant by *SOD1* expression in motorneurons.
a , Adult males (0-48 h old) homozygous for *Sodx39* and also bearing different combinations of HS and D42-GAL4 transgenes were maintained at 25 °C in shell vials (10 flies per vial) containing standard cornmeal agar medium. The starting population size for each genotype was 50 flies. Flies were scored daily for survivorship and transferred to fresh vials every two days. **b** , Gene-dosage effects on restoration of adult lifespan. Adult males (0-48 h old) homozygous for *Sodx39* and also bearing one or two copies each of HS1 and the D42-GAL4 activator were constructed and lifespan studies were conducted as in (a). The starting population sizes were 180, 335 and 70 for the 0-dose, 1-dose and 2-dose genotypes, respectively. The 0-dose control bears two copies of HS1 but no D42-GAL4 activator. The data presented are representative of at least two separate experiments.

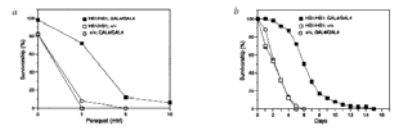
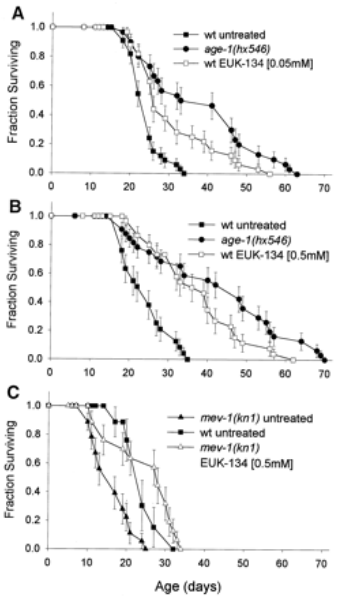


Figure 6. Expression of *SOD1* in motorneurons confers resistance to oxidative stress in *Sod* null mutants.
a , Resistance to paraquat. Adult males (0-48 h old) homozygous for *Sodx39* and also bearing different combinations of UAS-HS and D42-GAL4 transgenes were maintained at 25 °C in shell vials containing filter pads saturated with aqueous paraquat and scored for survival after 24 h. Each point represents 50 flies (5 vials of 10 flies each). **b** , Resistance to ionizing radiation. Adult males (24-48 h old) homozygous for *Sod*^{x39} and also bearing different combinations of UAS-HS and D42-GAL4 transgenes were exposed to 100 kRad -radiation (190 min at 520 Rads/min in a cobalt^{60} source) and then maintained at 25 °C in shell vials containing standard cornmeal agar medium and scored daily for survivorship. The data are representative of at least two separate experiments.

Nature Genetics **19**, 171 - 174 (1998)

Extension of Life-Span with Superoxide Dismutase/Catalase Mimetics



Gordon J. Lithgow

Buck Institute for Age Research

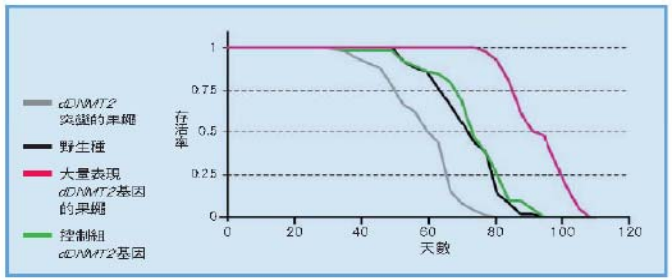
To test the oxygen radical theory of aging by the development of synthetic catalytic compounds that ameliorate oxidative stress in several disease modelsand partially rescue mice that are mutant for mitochondrial superoxide dismutase (SOD). tested the effect of two mimetics, EUK-8 and EUK-134, on life-span in *Caenorhabditis elegans*. In vitro, these compounds exhibit both SOD- and catalase-like activities (they are SOD/catalase mimetics). EUK-134 is an analog of EUK-8, with increased catalase activity and equivalent SOD activity

the effects of EUK-134 on the life-span of a mutant worm strain that exhibits accelerated aging. Mutation of the *mev-1* gene, encoding the cytochrome b subunit of succinate dehydrogenase (complex II) of the electron transport chain, results in an elevated accumulation of oxidative damage during aging, an increased sensitivity to oxygen, and a life-span shortened by 37% ($P < 0.0001$; Fig. 1C) (19, 20). Treatment with 0.5 mM EUK-134 restored a normal life-span to the *mev-1(kn1)* mutants by increasing their life-span by 67% ($P < 0.0001$; Fig. 1C). These results are consistent with amelioration of an endogenous and chronic oxidative stress.

Figure 1. Kaplan-Meier survival curve (±SE) of wild-type (wt) and *mev-1*(*kn1*) adult worms treated with SOD/catalase mimetics. Synchronously aging hermaphrodite worms were cultured in S medium with *Escherichia coli* as a food source (17). Worms were scored as dead when they failed to respond to repeated touching with a platinum wire pick. (**A**) Mean life-span (±SEM) in days of strain N2 (wild-type) = 24 ± 1 (solid squares); of strain TJ1052 [*age-1(hx546)*] = 38 ± 2 (circles); and of strain N2 (wild-type) treated with 0.05 mM EUK-134 = 31 ± 3 (open squares). (**B**) Mean life-span (±SEM) in days of strain N2 (wild-type) = 24 ± 1 (squares); of strain TJ1052 [*age-1(hx546)*] = 41 ± 3 (circles); and of strain N2 (wild-type) treated with 0.5 mM EUK-134 = 37 ± 2 (open squares). (**C**) Mean life-span (±SEM) in days of strain N2 (wild-type) = 24 ± 2 (squares), $n = 7$ worms; of strain *mev-1*(*kn1*) = 15 ± 1 (solid triangles), $n = 19$ worms; and of strain *mev-1(kn1)* treated with 0.5 mM EUK-134 = 25 ± 2, $n = 16$ worms. Very similar results were obtained in independent experiments.

Science, Vol 289, Issue 5484, 1567-1569 , 1 September 2000

- 脊椎動物的細胞中皆有所謂DNA甲基化酶(DNMT1)，它們在個體發育、染色體結構及基因調控上，都扮演了重要的角色。
- 1999年，從果蠅的基因組序列資料庫中，找到了dDnmt2蛋白的序列，它和脊椎動物的各類DNA甲基化後半段序列類似。
- 更有趣的是，dDNMT2如果突變，則果蠅生命變短；如果過量表現這種蛋白質，則果蠅生命會增加30~50%（見下圖）。
- 關於dDNMT2基因身爲長壽基因所進行的機制，目前最確定的是，它會增加果蠅細胞中的熱休克蛋白含量，所以可能機制之一是它讓細胞可對抗環境壓力。



在果蠅中，利用跳躍子插入dDNMT2 基因所造成的突變，其壽命較野生種短。而利用UAS-GAL4系統大量表現dDNMT2基因的果蠅，相較於野生種及控制組有較長的壽命。

- 影響壽命長短的基因非常多，而且它們極可能皆可調控或參與一個以上的生物過程；某些不同的長壽或老化基因還牽涉到同樣的生物過程。在延長壽命的研究上，目前不少實驗室及生物科技公司皆已在發展藥物，經由調控這些長壽或老化的基因或其產物的活性，這些研究發展於可見的將來，在增進人類健康與延年益壽的醫藥領域上，必定佔有重要的地位。

解密長壽基因
Unlocking the Secrets of Longevity Genes

- 有一群特別的基因，在生物體處於艱困的時期，會協助身體的防衛，這群基因能夠增進個體的健康和壽命。如果想要延年益壽、減少老年病痛，關鍵就在於解開這群基因作用的奧秘。

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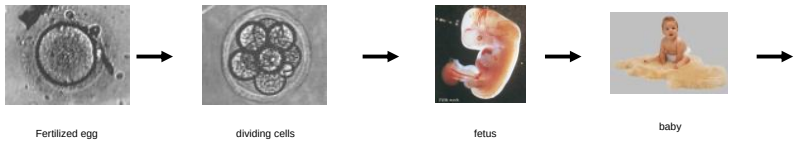
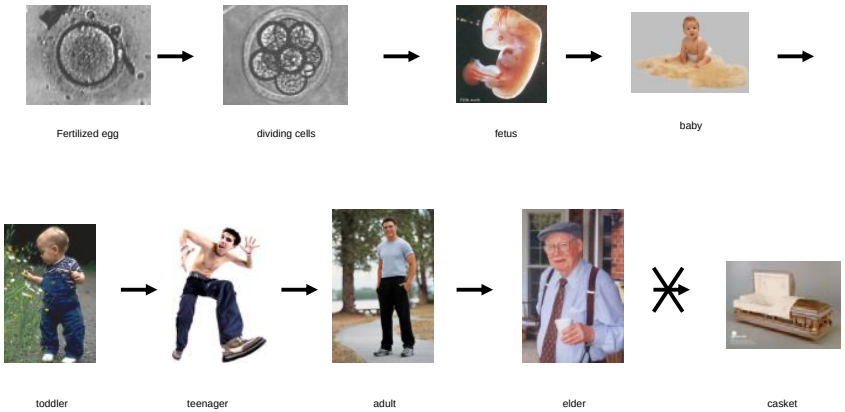
From development to aging

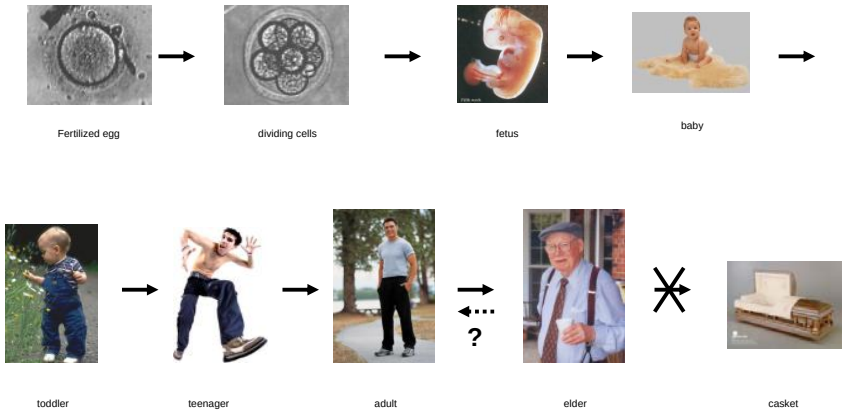


From development to aging



Long-lived

From development to aging



forever young? **Long-lived**

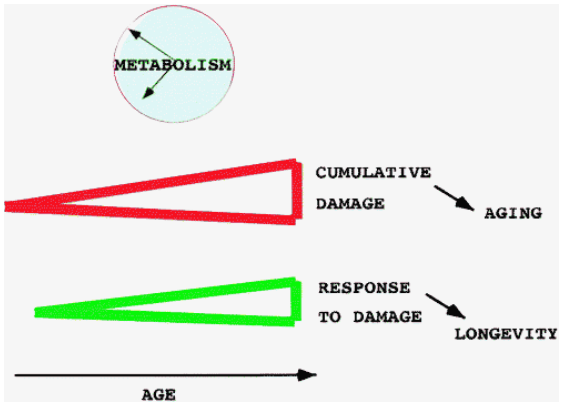


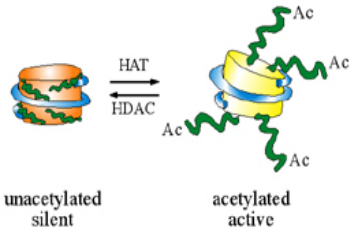
Figure 1. Life Span Is Determined by the Balance of Two Opposing Processes
Metabolism leads to the accumulation of damage (red), thus causing aging. Compensatory responses (green) limit or repair the damage, thus promoting longevity.

- 最近科學家發現了許多基因，取的名字像是密碼一般：daf-2、pit-1、amp-1、clk-1和p66Shc，它們會影響實驗動物的抗壓能力和壽命，顯示可能與生物體在逆境下生存的基本機制有關（參見第28頁〈延年益壽的基因作用途徑〉）。但作者實驗室將研究焦點集中在名爲SIR2的基因，在所有測試過的生物體內，從酵母菌到人類，都有SIR2基因的各式版本。而且將酵母菌、線蟲和果蠅等各種生物體內加入額外的SIR2基因後，牠們的壽命都增長了。他們的實驗室正在測試這個基因對較大動物（像是小鼠），是否也有類似的效應。
- 在首先鑑定出來的長壽基因中，SIR2研究得最詳盡，因此在這裡作者將著眼於它的作用機制。它顯示了基因調控的生存機制是如何延長壽命、促進健康，而且有越來越多的證據顯示，SIR2可能就是這套機制的中樞調控者。

Silent information regulator 2

[DEFINITION] NAD-dependent histone deacetylase sir2 (Regulatory protein sir2) **(Silent information regulator 2).**

[FUNCTION] Involved in silencing within the mating-type region, at the telomeres, and according to Ref.4 also within centromeric DNA regions. Required for the localization of swi6 to the telomeres, silent mating type region, and according to Ref.4 to the centromeric DNA regions. According to Ref.1 not required for the localization of swi6 to centromeric foci. Deacetylates histone H3 on Lys-9 and Lys-16 of histone H4. This has a direct role in heterochromatin assembly.



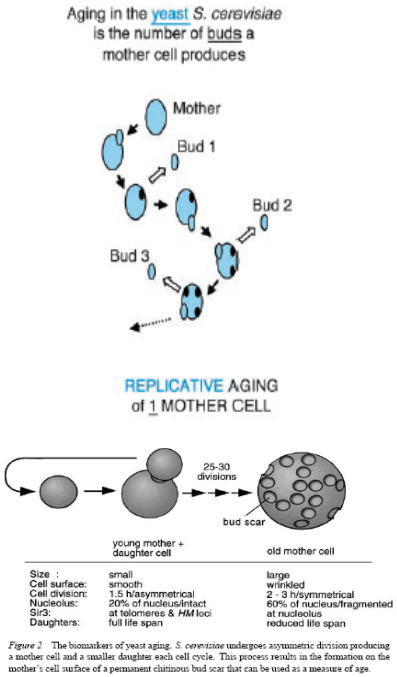


Figure 2 The biomarkers of yeast aging. *S. cerevisiae* undergoes asymmetric division producing a mother cell and a smaller daughter each cell cycle. This process results in the formation on the mother's cell surface of a permanent chitinous bud scar that can be used as a measure of age.

- **保護基因組**
- 作者會發現SIR2是一個長壽基因，最初是因爲想探究讓烘焙用的酵母菌變老的原因，是否有一個基因控制了這種簡單的生物的老化過程？當時許多人認爲我們想從了解酵母菌壽命，來得知有關人類壽命資訊的想法有些荒謬。酵母菌的老化，是計算母細胞在死去前分裂形成子細胞的次數，一個酵母菌的壽命極限大約是分裂20次。

作者賈倫堤開始研究時，先篩選壽命特別長的酵母菌落，希望能從中找出讓它們長壽的基因。當時發現有一個菌落帶有突變的SIR4基因。SIR4基因所製造的蛋白質，會與Sir2酵素和其他蛋白質一起組成複合體。而這個酵母菌落的SIR4基因突變，會造成Sir2蛋白質聚集在酵母菌基因組上一段具有許多重複序列的區域，這段區域內含有建造蛋白質工廠的基因：核糖體DNA（rDNA）。酵母菌基因組內有上百個重複的rDNA，由於重複序列常有彼此「重組」的傾向，因此不容易維持穩定。這種重組現象會造成許多人類疾病，像是癌症和杭丁頓氏症。我們的研究顯示，酵母菌母細胞的老化正是因爲rDNA不穩定的型式所造成的，而Sir蛋白質則可減緩這種不穩定狀態。

Aging in budding yeast is measured by the number of mother cell divisions before senescence.

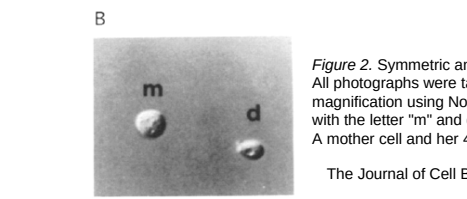
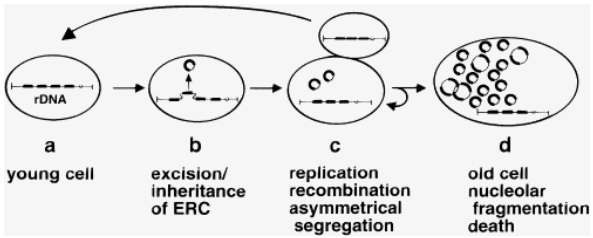


Figure 2. Symmetric and asymmetric cell divisions. All photographs were taken at 1,000x magnification using Nomarski optics. Mother cells are labeled with the letter "m" and daughters with the letter "d7 (B) A mother cell and her 42nd daughter to the right.

The Journal of Cell Biology, 1994, Volume 127, p1985-1993

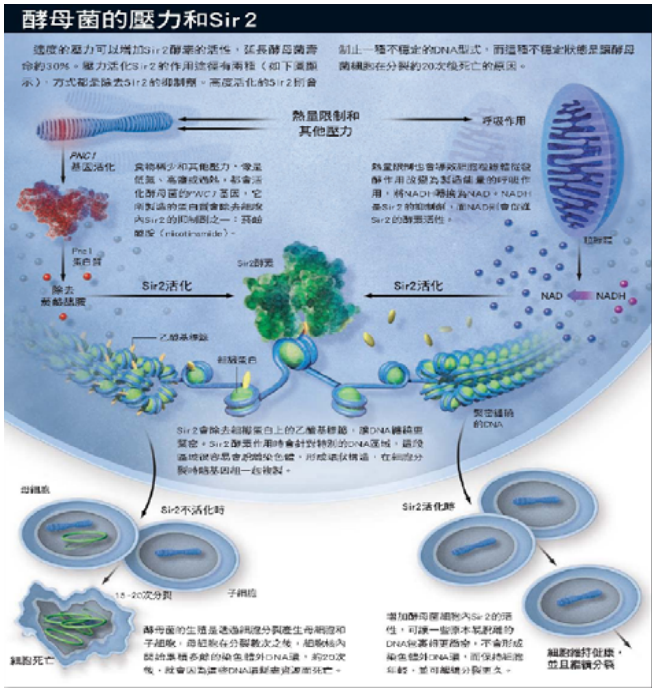


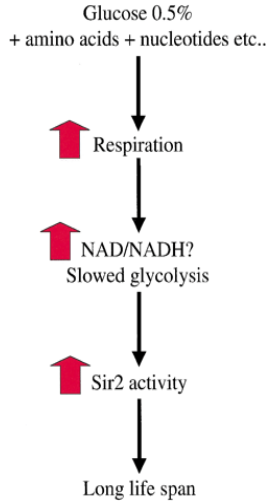
Model of Yeast Aging Due to Accumulation of Extrachromosomal rDNA Circles (ERCs).

Cell, 1997, Vol 91, Pages 1033-

•酵母菌母細胞在分裂多次後，會讓額外的rDNA脫離基因組，形成「染色體外rDNA環(ECR)」，一種特殊的rDNA不穩定狀態。染色體外rDNA環會和染色體一樣，在細胞分裂前進行複製，但分裂後都留在母細胞的細胞核內，於是母細胞內累積的染色體外rDNA環越來越多，敲響了母細胞的喪鐘。可能是這些染色體外rDNA環耗費太多資源，終於導致細胞無法複製自己的基因組而造成的。

- 當酵母菌細胞內加入一個額外的SIR2基因，就可以抑制rDNA環的形成，而細胞壽命則增長30%。這項發現可以解釋爲什麼SIR2在酵母菌內可做爲長壽基因。但驚奇的是，不久後作者發現額外的SIR2基因，也可讓線蟲的壽命延長50%。讓作者如此驚訝的理由，除了因爲這兩種生物在演化上相距極遠，還因爲成熟線蟲體內僅含有不會分裂的細胞，因此酵母菌複製的老化機制解釋，並不適用於線蟲。作者很想知道SIR2基因到底有什麼作用。
- 作者很快就發現，SIR2基因製造的酵素有著全新的活性。位於細胞核內的染色體DNA，平常是纏繞在組織蛋白（histone）上的，而組織蛋白上常會帶有化學標記，像是乙醯基，這些標記決定了DNA纏繞的緊實度。如果移除乙醯基，就可以讓整個纏繞的結構更緻密，使得一些酵素無法接觸到DNA（像是造成rDNA脫離染色體的酵素）。對這些包裹在去除乙醯基組織蛋白上的DNA，作者會用「沈寂」來形容，因爲基因組的這段區域不會活化。
- 作者之前就已經發現Sir蛋白質與基因的沉寂有關，事實上，SIR就是「沉寂資訊的調節者」（silent information regulator）的英文縮寫。Sir2是負責移除組織蛋白上乙醯標記的酵素之一，但作者發現Sir2作用的獨特之處，是其酵素活性絕對需要一個無所不在的小分子：菸鹼醯胺腺嘌呤二核苷酸（NAD），NAD是許多細胞代謝反應的輔酶。發現Sir2和NAD的關聯讓作者非常興奮，因爲它讓Sir2的活性與代謝連接了起來，因此可解釋飲食熱量限制與老化的關係。





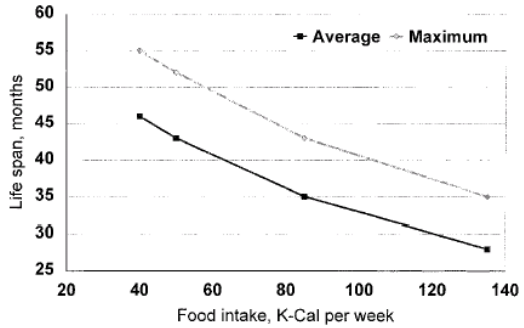
CR can be imposed in yeast by reducing the glucose concentration in the media from the usual 2% to 0.5% (Fig. 2; Lin et al. 2000). Because cells continue to feed on yeast extract plus peptone, which are rich in amino acids, nucleotides, and vitamins, the growth rate remains rapid as glucose levels are lowered. Thus, the reduction in glucose from 2% to 0.5%, although modest, likely imposes a state of partial energy (ATP) limitation. Other dietary restriction protocols, which also limit amino acids and other nutrients (Jiang et al. 2000, 2002), drastically slow the growth rate and may make it more difficult to impose energy limitation.

Under this conditions of CR, mother cells divide ~30% more times. ***This additional life span does not occur in a sir2 mutant or in strains in which NAD synthesis is reduced*** (Lin et al. 2000). Therefore, the activity of Sir2p is required to deliver the long life span by CR, and indeed, the silencing activity of Sir2p was shown to increase in CR cells.

Figure 2. Calorie restriction triggers a regulatory response in yeast

- 限制熱量與延長壽命
- 最有名的延長壽命方法，是限制一隻動物攝取的熱量。這個方法發現已超過70年，仍是唯一嚴密證明過的有效方法。熱量限制法一般是讓生物的飲食比該物種正常量少**30~40%**，從小鼠、大鼠到狗，可能還包括靈長類，在限制飲食下，不僅可以活得較久，而且也遠比一般動物健康，同時可以避免罹患癌症、糖尿病、甚至神經退化疾病等大多數老年疾病。這些動物的生存力似乎特別強，唯一顯見的缺點就是有些動物會失去生育力。

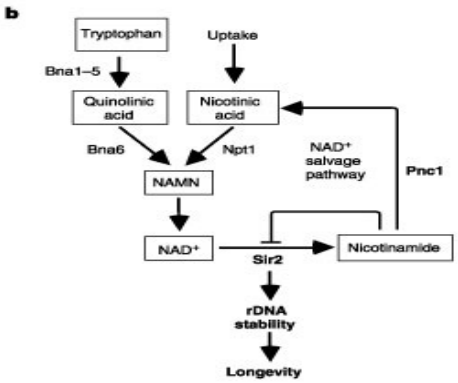
Prolong life span of mouse by reducing intake calorie



- 幾十年來，了解熱量限制法的作用機制，並開發能促進這種健康效應的藥物，一直是科學家追尋的目標（請參見2002年10月號〈尋覓抗老藥丸〉）。過去人們一直簡單的將熱量限制延緩老化的現象，歸因於減緩代謝（細胞利用能源分子產生能量的作用），而減少了有毒副產物。

  但這觀點目前看來並不正確，限制熱量並不會減緩哺乳動物的代謝，在酵母菌和線蟲中，代謝狀況反而會改變並且加快。因此作者相信，限制熱量的飲食就像食物稀少的自然狀況一樣，對生物來說是一種壓力，可激發生物的防衛反應，以增加生存的機會。哺乳動物對壓力的反應包括了改變細胞保衛、修護、能量製造和凋亡（計畫性細胞死亡）。作者想知道Sir2是否與這些改變有關，於是作者先檢查簡單生物在限制熱量的飲食中，Sir2扮演的角色。

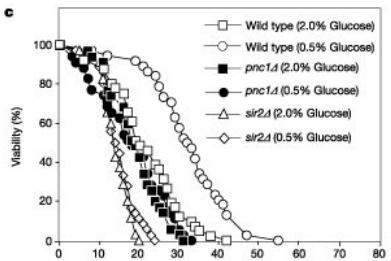
NAD+ synthesis pathway



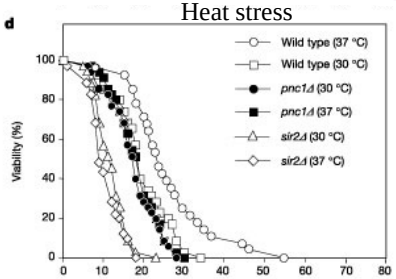
- 作者發現當食物有限時，酵母菌有兩個反應路徑會提高細胞內Sir2的酵素活性。其一，熱量限制會啓動PNC1這個基因，製造清除細胞內菸鹼醯胺（nicotinamide）的酵素，菸鹼醯胺類似維生素B3，平常會抑制Sir2活性。由於PNC1在其他已知可延長酵母菌壽命的輕微壓力下也會活化，像是環境溫度升高或鹽份增加，正好與作者認爲熱量限制是一種壓力因子的想法相符。

  而飲食限制誘導酵母菌Sir2活性的第二個途徑是呼吸作用。細胞在這生產能量的過程中，也會將NADH轉變爲NAD，這使得可活化Sir2的NAD增加，同時減少會抑制Sir2酵素的NADH，因此改變細胞的NAD/NADH比例，會大幅影響Sir2的活性。

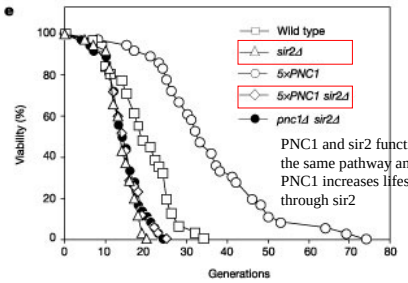
CR



Heat stress

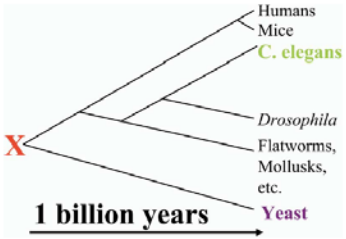


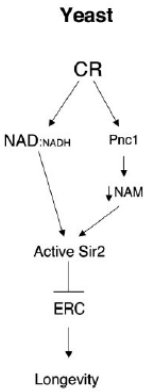
Non-stress condition

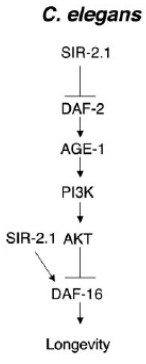


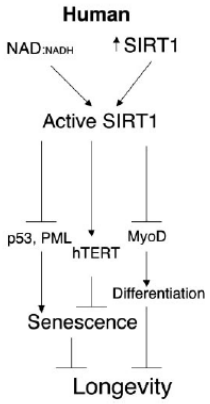
PNC1 and sir2 function in the same pathway and PNC1 increases lifespan through sir2

PNC1 is necessary for lifespan extension by CR and heat stress, and additional PNC1 is sufficient to mimic these stimuli









The role of *SIR2* genes in determining life span has been conserved in yeast and *C. elegans*.

This suggests that a *SIR2*-like gene must have carried out this function in the ancestral precursor organism of yeast and *C. elegans* (X) about one billion years ago.

Ageing

A toast to long life

Toren Finkel

Reducing food intake increases lifespan in many species. A small molecule that occurs naturally in plants seems to mimic the beneficial effects of caloric restriction and extend longevity in yeast.

Figure 1 A quest for longevity. Five hundred years ago, the Spanish explorer Ponce de León drank his way around the Florida coast during his expedition to find the legendary fountain of youth.

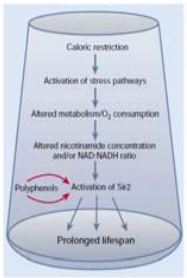


Figure 2 The pathway to long life. When yeast cells are deprived of food (caloric restriction), stress pathways are activated and the cells are forced to derive energy from alternative substrates. This produces alterations in oxygen consumption, which in turn affects the ratio of oxidized to reduced forms of nicotinamide adenine dinucleotide (NAD:NADH) or the concentration of its derivative nicotinamide. NAD stimulates the activity of Sir2, which in turn chemically modifies several proteins that are involved in cellular processes affecting longevity. Howitz *et al.*[1] have found that plant polyphenols directly activate Sir2 and seem to mimic the beneficial effects of food restriction. Related pathways may exist in higher organisms.

Using several chemical 'libraries', these investigators discovered two related compounds that each stimulated Sir2 activity. Both compounds belong to a family of molecules called polyphenols — products of metabolism in plants. One of the most widely studied of these compounds is **resveratrol**, a plant polyphenol that is abundant in red wine and is reputed to underlie many of wine's health related benefits.

Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan

Konrad T. Howitz[1], Kevin J. Bitterman[2], Haim Y. Cohen[2], Dudley W. Lamming[2], Siva Lavu[2], Jason G. Wood[2], Robert E.Zipkin[1], Phuong Chung[1], Anne Kisielewski[1], Li-Li Zhang[1], Brandy Scherer[1] & David A. Sinclair[2]

NATURE |VOL 425 | 11 SEPTEMBER 2003

STACs: sirtuin-activating compounds

白藜蘆醇

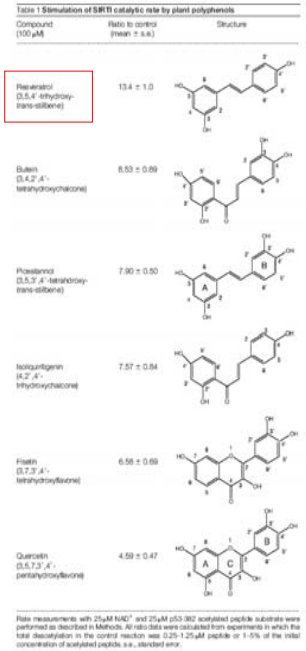


Table 1 Stimulation of SIRT1 catalytic rate by plant polyphenols

Compound (100 μM)	Ratio to control (mean ± s.e.)	Structure
Resveratrol (3,5,4′-trihydroxy-trans-stilbene)	13.4 ± 1.0	
Butein (3,4,2′,4′-tetrahydroxychalcone)	8.53 ± 0.69	
Piceatannol (3,5,3′,4′-tetrahdroxy-trans-stilbene)	7.90 ± 0.50	
Isoliquiritigenin (4,2′,4′-trihydroxychalcone)	7.57 ± 0.84	
Fisetin (3,7,3′,4′-tetrahydroxyflavone)	6.58 ± 0.69	
Quercetin (3,5,7,3′,4′-pentahydroxyflavone)	4.59 ± 0.47	

Rate measurements with 25 μM NAD^+ and 25 μM p53-382 acetylated peptide substrate were performed as described in Methods. All ratio data were calculated from experiments in which the total deacetylation in the control reaction was 0.25–1.25 μM peptide or 1–5% of the initial concentration of acetylated peptide. s.e., standard error.

Fountain of youth juice

Sirtuin activators mimic caloric restriction and delay ageing in metazoans

Jason G. Wood, Blanka Rogina, Siva Lavu, Konrad Howitz, Stephen L. Helfand, Marc Tatar, and **David Sinclair**

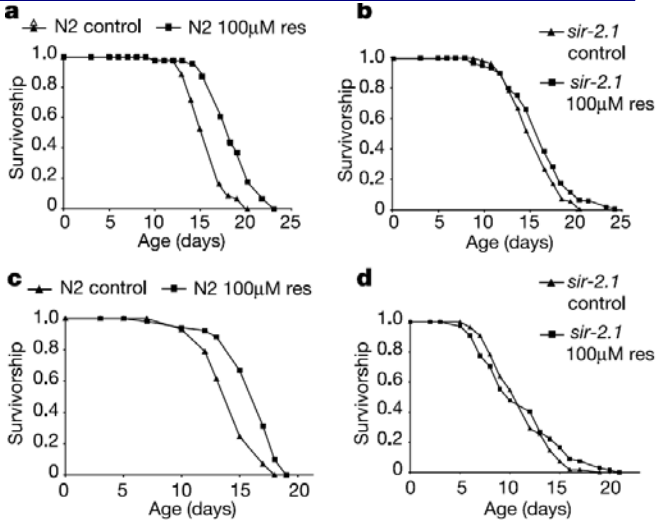
Nature. 2004;430(7000):686-9

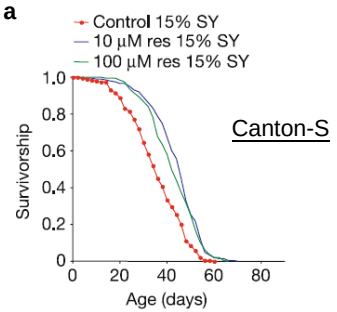
Lifespan extension induced by resveratrol requires SIR-2.1 in *C. elegans*

wildtype | *sir2.1* mutant

heat-killed *E. coli.*

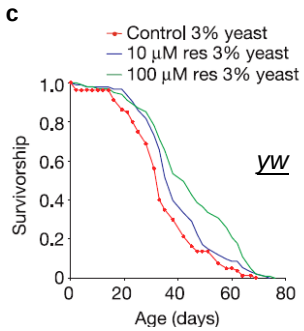
live *E. coli.*





Canton-S

Resveratrol and other STACs extend *Drosophila* lifespan



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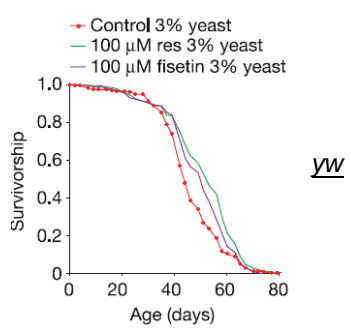

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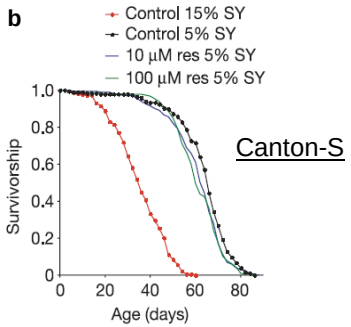
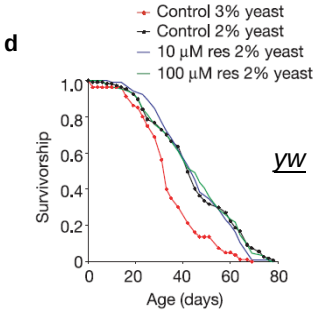


Canton-S

Resveratrol can't further extend fly lifespan in CR condition



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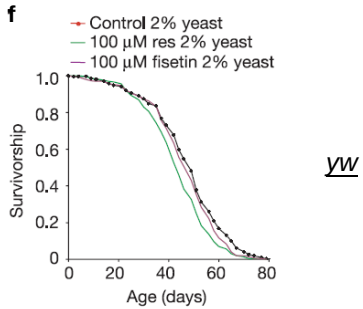

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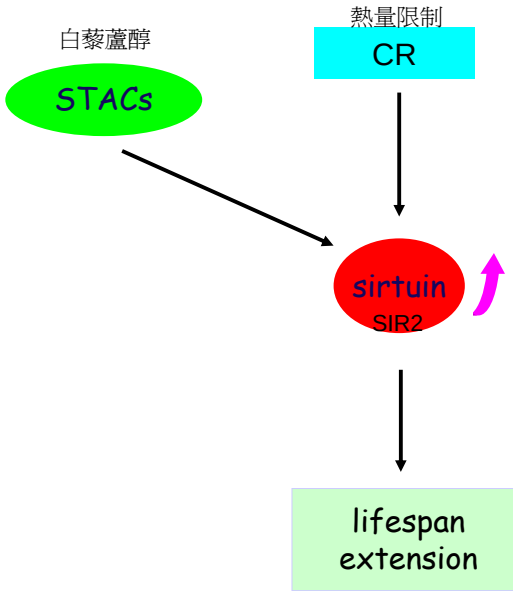
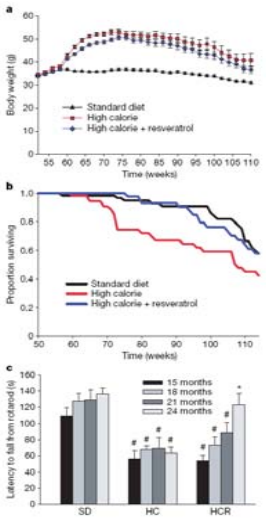


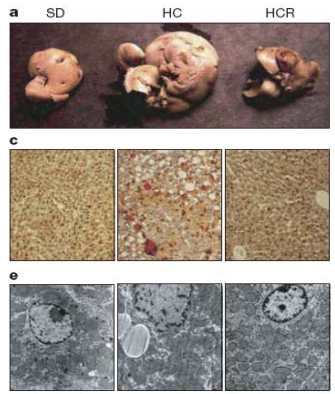
French paradox

Despite a high-fat diet, people in France suffer about 40% less cardiovascular disease than expected

Good vintage: a compound found in red wine called resveratrol might explain why the French have fatty diets but long lives.

Resveratrol improves health and survival of mice on a high-calorie diet





Nature **444**, 337-342 (16 November 2006)

SIRT1協調全身保護機制

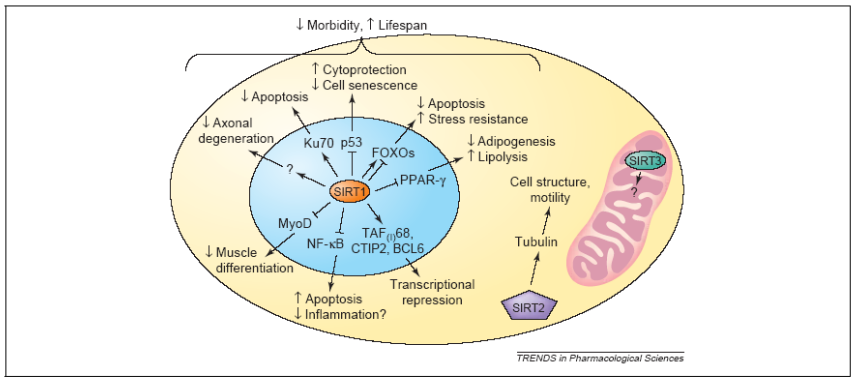
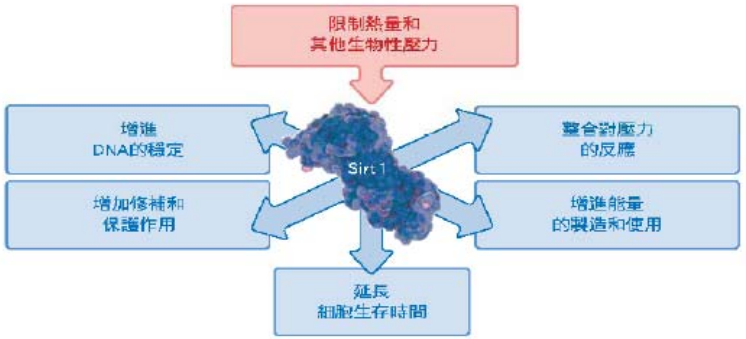


Figure 5. Cellular targets of mammalian sirtuins. Nuclear SIRT1 targets several chromatin-interacting proteins with key roles in transcription, stress response and death. Regulation of these proteins by SIRT1-dependent deacetylation might result in enhanced cellular resistance to stress, reduced morbidity and lifespan extension. SIRT2 is mainly cytoplasmic and deacetylates tubulin, suggesting a role in microtubule organization in addition to cell structure and motility. SIRT3 is a mitochondrial deacetylase with unknown functions. Pharmacological modulation of sirtuin activity by enzymatic activators or inhibitors can therefore significantly affect cellular functioning and be harnessed to therapeutic interventions (see main text for further details). Abbreviations: PPAR-γ, peroxisome proliferator-activated receptor γ.

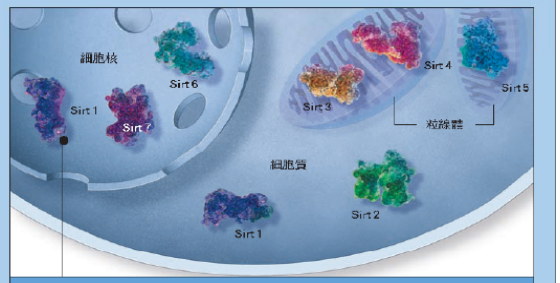


哺乳動物熱量限制的健康和延壽效應，似乎主要都是透過Sirt1酵素來負責統籌各項變化。食物稀少和其他生物性壓力會提高Sirt1的活性，然後改變細胞內的各種活性。Sirt1還可促進胰島素等特定訊息分子的製造，整合動物體對壓力的反應，這些都是透過Sirt1修飾其他蛋白質達成的（參見下頁〈細胞內的Sirtuin〉）。

細胞內的Sirtuin

Sirt1是研究最詳盡的Sirtuin蛋白質，不過卻不是哺乳動物中唯一的Sirtuin蛋白質。其他與*SIRT1*相關的基因，也會製造類似的酵素，在細胞內不同位置作用。Sirt1在細胞核和細胞質中很活躍，會除去其他蛋白質上的乙醯基，而改變這些蛋白質的行為。在其作用目標中，有許多可以直接活化基因的轉錄因子，或能夠調節轉錄因子的蛋白質（參見右下），這使得Sirt1擁有調節各項重要細胞功能的控制權。

科學家才剛開始確認其他Sirtuin的功用，並探討它們是否也能影響壽命。舉例來說，Sirt2已知能調節構成細胞支架的微管（tubulin），可能會影響細胞分裂。Sirt3在細胞發電廠粒線體中活動，可能參與了體溫的調節。Sirt4和Sirt5的功能未知，Sirt6基因突變時會有提早老化的現象。



Sirt1的作用目標

FoxO1、FoxO3和FoxO4：細胞防衛和葡萄糖代謝相關的轉錄因子。

組蛋白H3、H4和H1：控制DNA緊緊形成染色體結構。

Ku70：促進DNA修復和細胞生存的轉錄因子。

MyoD：促進肌肉生長和組織修補的轉錄因子。

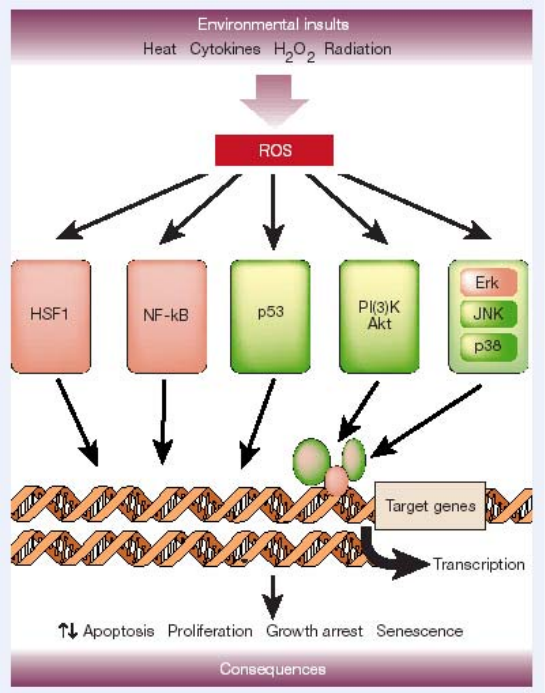
NCoR：一種調節分子，可以影響脂肪代謝、發炎和其他調節因子（像是PGC-1α）的基因。

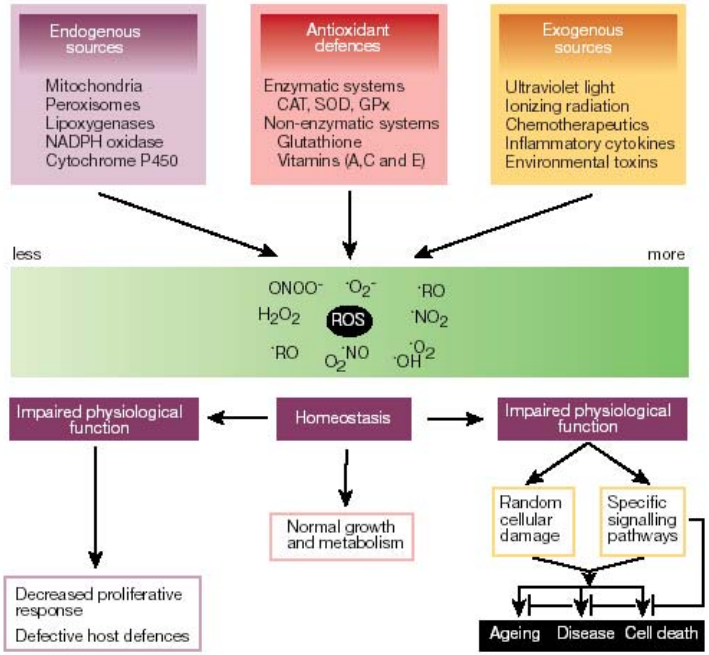
NF-κB：控制發炎、細胞生存和細胞生長的轉錄因子。

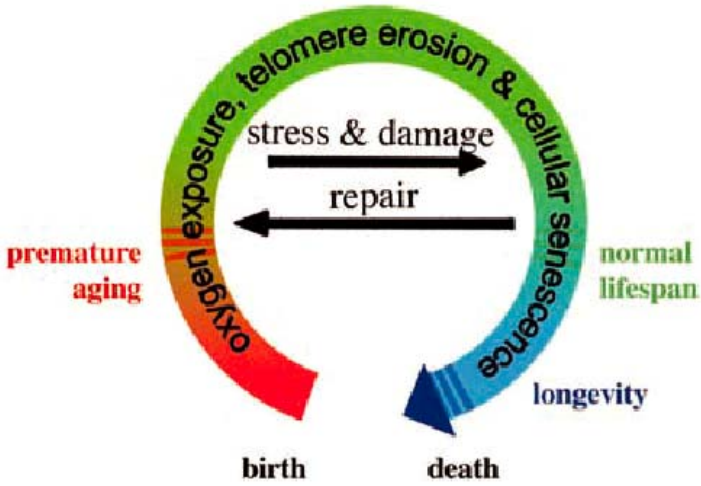
P300：調節因子，促使組蛋白加上乙醯基標籤。

P53：可引發受傷細胞計畫性死亡的轉錄因子。

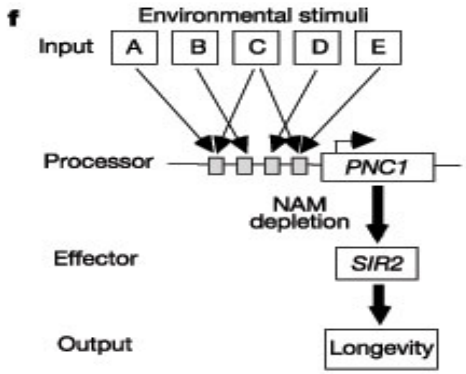
PGC-1α：控制細胞呼吸作用的調節因子，可能在肌肉的發育過程中也扮演有重要角色。







Correlation between stress, damage, ageing and longevity.



提高壽命的極限

■負責生物因應惡劣環境變化的基因如果活躍，能夠暫時強化細胞以維持生存。

■因應壓力的反應長期活躍，對有些生物而言，有延長壽命、減少疾病的功效。

■Sirtuin是一群基因，可能是調控壓力生存機制的中樞。

■了解Sirtuin如何促進健康、延長壽命，可以幫助我們開發疾病療方，最終讓人類活得更久、更健康。

Eat your hot-dog and have it

Reducing your calorie intake makes you live longer — if you're a rat or a worm. **Laura Spinney** asks whether the same holds for humans — and if it does, whether the benefits could be put in a pill.

or

NATURE,Vol 441,15 June, 2006

Eat your hot-dog and have it

Reducing your calorie intake makes you live longer — if you're a rat or a worm. **Laura Spinney** asks whether the same holds for humans — and if it does, whether the benefits could be put in a pill.

or

+

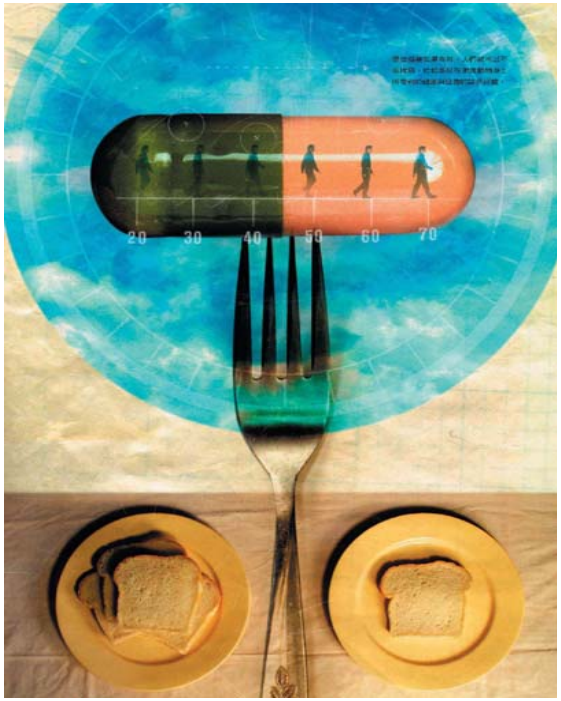
白藜蘆醇

NATURE,Vol 441,15 June, 2006

尋覓抗老藥丸
The Serious Search for an Anti-Aging Pill

作者／連恩 (Mark A. Lane) 、殷格朗 (Donald K. Ingram) 、羅斯 (George S. Roth)
譯者／黃榮棋

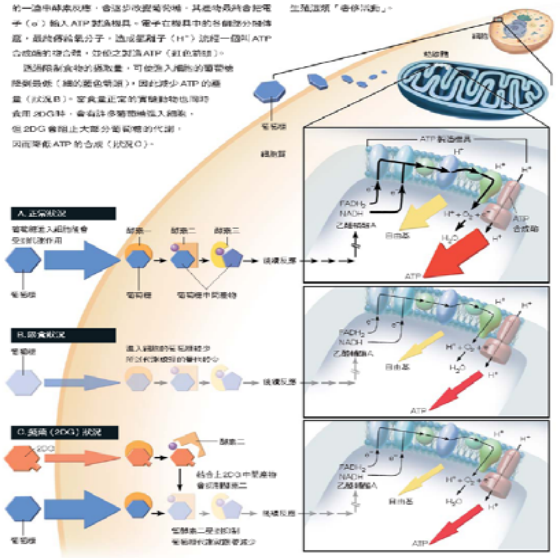
雖說目前市面上還沒有任何經過科學家實驗證實的長生不老藥，科學家在尋覓抗老藥丸的道路上，卻是馬不停蹄。想要延年益壽、永保青春活力？限制熱量的攝取可能相當有效，但若是有一種不必挨餓也能抗老的藥丸，豈不更妙？



- 老化，是一種當人年事漸長，體內的分子與細胞損傷累積到一個程度，而導致對疾病失去抵抗力的現象。但是，有一種干預對好幾種動物都十分有效，那就是低熱量但營養均衡的飲食，它會延長實驗動物的壽命與健康的生命期。這些研究發現暗示著，限制熱量的攝取可能也會延緩人類老化。

不幸的是，若想達到最佳效果，人們恐怕必須減少食物中約30%的熱量攝取，等於是從每天2500大卡降到1750大卡。一般人很少能夠遵守這麼嚴苛的養生之道，何況還必須年復一年持續下去。但要是有人可以發明一種藥丸，既可模擬限食的生理效應，又不必強迫人們挨餓，豈不妙哉？這種我們稱之爲「限食擬藥」（caloric-restriction mimetic）的東西，是否能讓人們健康得久些，延遲老年相關疾病（像是糖尿病、動脈硬化、心臟疾病及癌症）的出現，直到生命終點？

作者最早在1990年代中期提出這個問題，當時無意間發現一種化學藥劑，似乎可以在齧齒動物身上重現限制熱量攝取的許多好處。從此之後，作者以及其他的研究人員，就一直在尋找能夠安全應用到人類身上的這種藥物。



可讓作者找到了！

約在線蟲結果發表的期間，作者開始搜尋文獻，希望能找到可以操弄餓鳥素分泌及敏感度，但又不會造成糖尿病或其相反結果（血糖過低）的方法。在1940~50年代之間，有研究提到一種稱爲「2-去氧-D-葡萄糖」（2-deoxy-D-glucose，以下簡稱2DG）的物質，曾用在齧齒動物癌症治療的實驗上，文獻同時提到血中餓鳥素濃度下降的情形。在更進一步的文獻考查之後，可終於找到了！

這個化合物顯然重現許多限食的典型反應，其中包括抑制腫瘤的生長（已略遜於眾所周知的延長壽命）、體溫下降、糖皮質素濃度上升，以及生殖週期數目減少。要是2DG真能模擬動物限食的諸多面向，我們想，或許2DG對人也會有同樣的結果。

作者計畫第一個2DG實驗的同時，也翻閱了文獻，想了解這個物質詳細的分子機制。從文獻得知，它會阻斷細胞中參與葡萄糖代謝的一個關鍵酵素。2DG的結構類似葡萄糖，所以很容易就進入細胞，同樣也會受到作用在葡萄糖的酵素所影響。但參與葡萄糖代謝後續幾個步驟的酵素，基本上會因2DG製造出來的中間產物而喪失功能。因此當酵素想要作用在2DG的中間產物時，就辦不到了；更甚者，連作用在正常葡萄糖中間產物的能力，也一併遭到破壞。

最終結果是，細胞從葡萄糖的代謝製造出來的產物變少了，正如限食降低了進入細胞的葡萄糖時所發生的情形一樣。某些葡萄糖的產物會成爲「ATP製造機具」的原料；ATP製造機具是由一系列的蛋白複合體組成，位於粒線體裡。沒有這些原料，製造的ATP就會比較少。原則上，2DG讓細胞陷入一種類似限食時的代謝狀態，即使進食量並沒有改變。只要ATP的量能夠滿足細胞最起碼的需求，那麼減少ATP製造機具的運作，顯然對身體有利。

爲什麼ATP製造機具減量生產可以幫助對抗老化？雖然不能說百分之百道盡，但有些想法。一個長久以來的理論，將老化歸咎於「自由基」，分子的產生，體內一大部分的自由基，是在ATP製造機具運作過程中釋放出來的，日積月累之後，這些化學反應能力超強的分子，據信會對細胞許多不同的構造造成永久性的傷害，包括負責製造ATP的蛋白複合體本身。或許2DG與限食都是透過降低ATP產生的速率，來降低自由基形成及細胞遭破壞的速率。

限食的好處

作者會想尋找限食擬藥，是因爲作者想更了解限食對身體的諸多效應。科學家早在60年前就已經知道限食的價值，因爲當時實驗發現，餵食低熱量食物的大鼠，平均活得比自由攝取食物的大鼠久，而且也比較不會產生年老大鼠常見的問題。除此之外，限食組的大鼠活得比對照組最老的大鼠還久。也就是說，不只是平均壽命，連最長壽命（可活最久的年齡）也增加了。各種干預方法，像是抗感染藥物，雖然可以增加族群的平均壽命，但只有降低身體老化速率的方法才能增加最長壽命。

大鼠的實驗結果已經重複過許多次，而且，從酵母菌到果蠅、蠕蟲、魚、蜘蛛、小鼠及倉鼠，也都有同樣的結果。但這類研究針對的都是與人類遭傳相去甚遠的短命生物，一直要到前陣子，才出現了針對接近人類的兩種靈長類（恆河猴與松鼠猴）的研究報告。這些持續進行中的長期研究顯示，靈長類的限食反應幾乎同齧齒類的一樣，這使作者更樂觀地相信：限食擬藥可以幫助人們。

猴子的研究計畫始於1980年代末期。當時作者在美國國家衛生研究院老化研究所所做的實驗，與1990年代初威斯康辛大學麥迪遜分校另一個研究團隊所做的實驗都證實：比起正常飲食的對照組動物，限食組猴子的體溫較低，胰島素的濃度也較低，而且某些荷爾蒙（像是會隨著年齡下降的脫氫表雄甾酮或硫酸脫氫表雄甾酮）仍維持在年輕時的濃度。

在代表老化的相關疾病方面，這些限食動物看來也比較健康。譬如說，牠們的血壓與三酸甘油酯含量比較低（表示得到心臟疾病的機會較低），血糖濃度也比較正常（表示得糖尿病的風險較低，糖尿病的特徵是不尋常的高血糖濃度）。此外，作者最近也指出，根據風險資料的統計，長期限食（將近15年）的恆河猴得慢性病的機會也較低。但想要知道限食是否會延長猴子的平均壽命及最長壽命（恆河猴一般活到24歲，有時可到40歲；松鼠猴一般活到19歲，但有時可到28歲），作者還必須對這些恆河猴及其他猴子做更久的追蹤研究才行。

Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease.

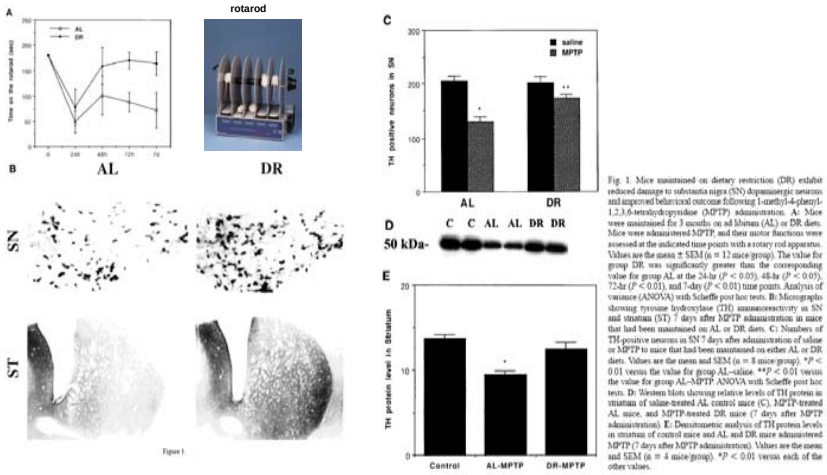


Fig. 1. Mice maintained on dietary restriction (DR) exhibit reduced damage to substantia nigra (SN) dopaminergic neurons and improved behavioral outcome following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. A: Mice were maintained for 3 months on ad libitum (AL) or DR diets. Mice were administered MPTP, and their motor functions were assessed at the indicated time points with a rotary rod apparatus. Values are the means ± SEM (n = 12 mice/group). The value for group DR was significantly greater than the corresponding value for group AL at the 24-hr ($P < 0.05$), 48-hr ($P < 0.05$), 72-hr ($P < 0.01$), and 7-day ($P < 0.01$) time points. Analysis of variance (ANOVA) with Scheffe post hoc tests. B: Micrographs showing tyrosine hydroxylase (TH) immunoreactivity in SN and striatum (ST) 7 days after MPTP administration in mice that had been maintained on AL or DR diets. C: Numbers of TH-positive neurons in SN 7 days after administration of saline or MPTP to mice that had been maintained on either AL or DR diets. Values are the means and SEM (n = 8 mice/group). *$P <$ 0.01 versus the value for group AL–saline. **$P < 0.01$ versus the value for group AL–MPTP. ANOVA with Scheffe post hoc tests. D: Western blots showing relative levels of TH protein in striatum of saline-treated AL control mice (C), MPTP-treated AL mice, and MPTP-treated DR mice (7 days after MPTP administration). E: Densitometric analysis of TH protein levels in striatum of control mice and AL and DR mice administered MPTP (7 days after MPTP administration). Values are the means and SEM (n = 4 mice/group). *$P < 0.01$ versus each of the other values.

Journal of Neuroscience Research 57:195–206 (1999)

限制熱量的攝取，體溫會降低、胰島素濃度也降低，某些荷爾蒙維持在年輕時的濃度，得到糖尿病、高血壓、心臟病、癌症的風險也相對降低。在大鼠與猴子的實驗中，就連平均壽命也提高了。

限食擬藥 2DG 會阻斷葡萄糖代謝中的一個關鍵酵素，因而減少了 ATP 的產生，造成類似限食的假象。ATP不多，自由基也跟著少了，細胞受到自由基破壞的程度自然減小，可能可以降低老化的速率。

要是證實抑制代謝真的可以延緩老化，科學家的下一個目標，就是要找出具有 2DG 的好處，且不易產生毒性、方便使用的物質，讓人們不必挨餓，就可以健健康康、輕輕鬆鬆永保青春。

WHAT DON'T WE KNOW?

How Much Can Human Life Span Be Extended

When Jeanne Calment died in a nursing home in southern France in 1997, she was 122 years old, the longest-living human ever documented. But Calment's uncommon status will fade in subsequent decades if the predictions of some biologists and demographers come true. Life-span extension in species from yeast to mice and extrapolation from life expectancy trends in humans have convinced a swath of scientists that humans will routinely coast beyond 100 or 110 years of age. (Today, 1 in 10,000 people in industrialized countries hold centenarian status.) Others say human life span may be far more limited. The elasticity found in other species might not apply to us. Furthermore, testing life-extension treatments in humans may be nearly impossible for practical and ethical reasons.

Just 2 or 3 decades ago, research on aging was a backwater. But when molecular biologists began hunting for ways to prolong life, they found that life span was remarkably pliable. Reducing the activity of an insulinlike receptor more than doubles the life span of worms to a startling—for them—6 weeks. Put certain strains of mice on near-starvation but nutrient-rich diets, and they live 50% longer than normal.

Some of these effects may not occur in other species. A worm's ability to enter a "dauer" state, which resembles hibernation, may be critical, for example. And shorter-lived species such as worms and fruit flies, whose aging has been delayed the most, may be more susceptible to life-span manipulation. But successful approaches are converging on a few key areas: calorie restriction; reducing levels of insulinlike growth factor 1 (IGF-1), a protein; and preventing oxidative damage to the body's tissues.

All three might be interconnected, but so far that hasn't been confirmed (although calorie-restricted animals have low levels of IGF-1).

Can these strategies help humans live longer? And how do we determine whether they will? Unlike drugs for cancer or heart disease, the benefits of antiaging treatments are fuzzier, making studies difficult to set up and to interpret. Safety is uncertain; calorie restriction reduces fertility in animals, and lab flies bred to live long can't compete with their wild counterparts. Furthermore, garnering results—particularly from younger volunteers, who may be likeliest to benefit because they've aged the least—will take so long that by the time results are in, those who began the study will be dead.

That hasn't stopped scientists, some of whom have founded companies, from searching for treatments to slow aging. One intriguing question is whether calorie restriction works in humans. It's being tested in primates, and the National Institute on Aging in Bethesda, Maryland, is funding short-term studies in people. Volunteers in those trials have been on a stringent diet for up to 1 year while researchers monitor their metabolism and other factors that could hint at how they're aging.

Insights could also come from genetic studies of centenarians, who may have inherited long life from their parents. Many scientists believe that average human life span has an inherent upper limit, although they don't agree on whether it's 85 or 100 or 150.

One abiding question in the antiaging world is what the goal of all this work ought to be. Overwhelmingly, scientists favor treatments that will slow aging and stave off age-related diseases rather than simply extending life at its most decrepit. But even so, slowing aging could have profound social effects, upsetting actuarial tables and retirement plans.

Then there's the issue of fairness: If antiaging therapies become available, who will receive them? How much will they cost? Individuals may find they can stretch their life spans. But that may be tougher to achieve for whole populations, although many demographers believe that the average life span will continue to climb as it has consistently for decades. If that happens, much of the increase may come from less dramatic strategies, such as heart disease and cancer prevention, that could also make the end of a long life more bearable. —JENNIFER COUZIN