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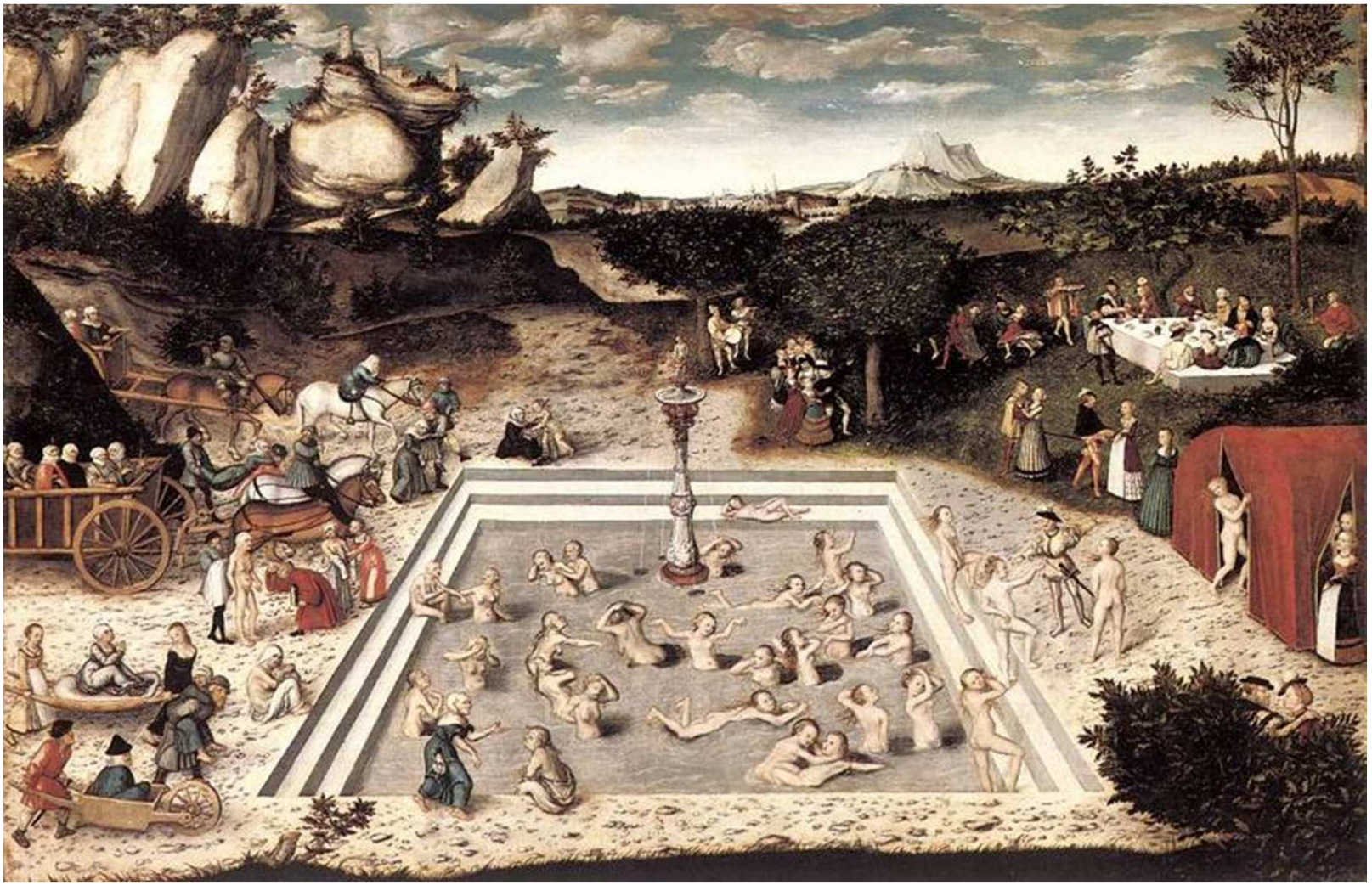
The Fountain of Youth -- Lucas Cranach (1546)

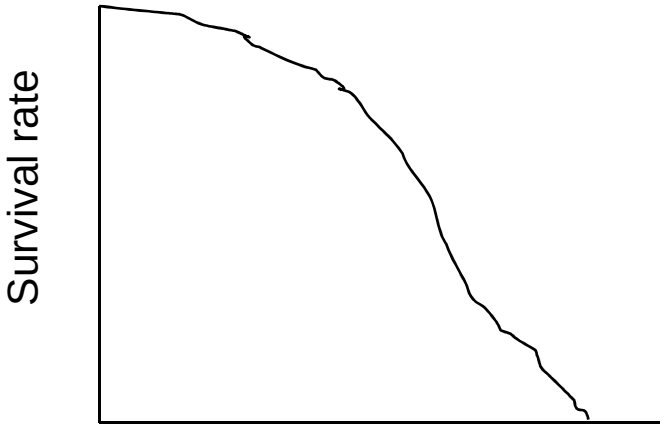
青春之泉



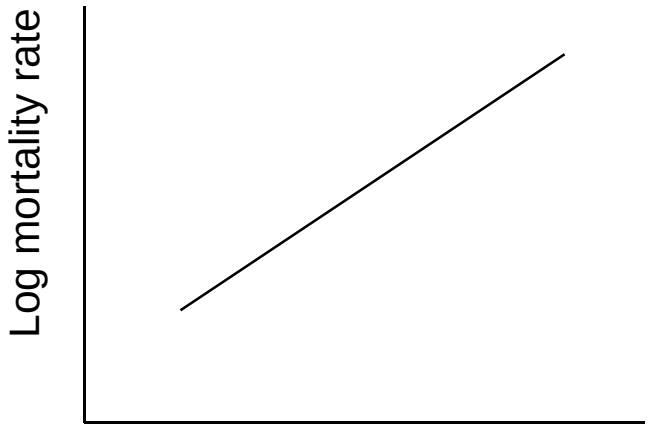
What is aging?

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

Lifespan



Mortality



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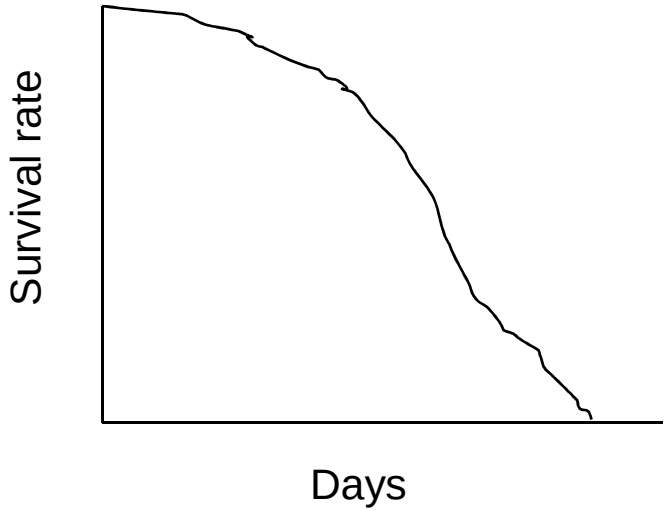
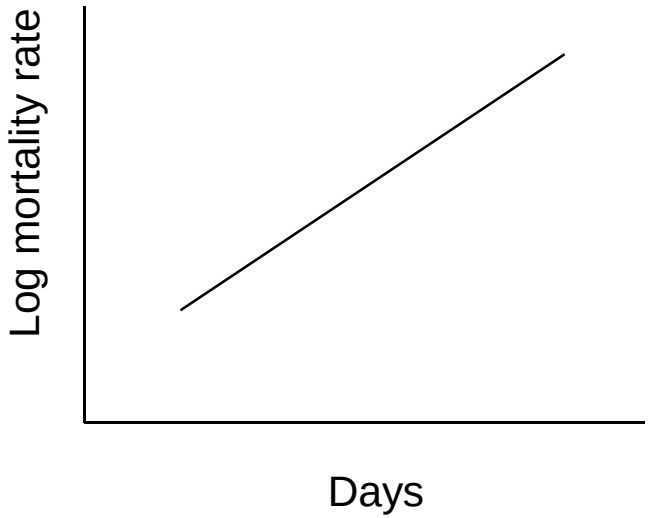




Aging theories

Evolutionary: Loss of selection

Mechanistic: Free radical (自由基)
Caloric intake (卡路里攝取)
Metabolic rate (代謝速率)
Hormone (激素)
Replicative senescence (細胞複製之衰老)
– telomere (端粒)

長生不死的夢想雖遙不可及，
但線蟲、果蠅和鴿子或許可以教導我們幾招延年益壽術。

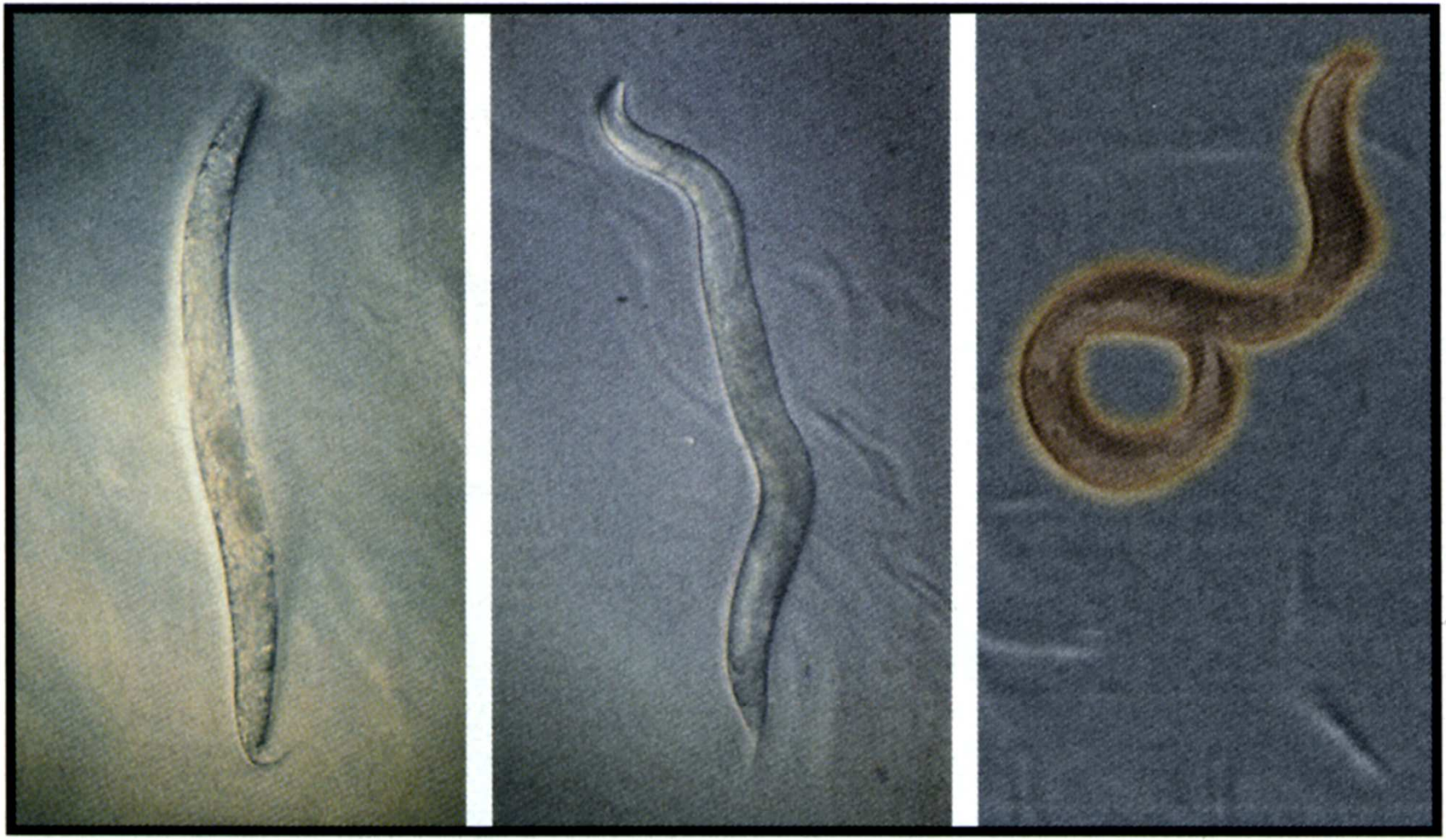
200歲的挑戰

科學人2007 永保青春特刊

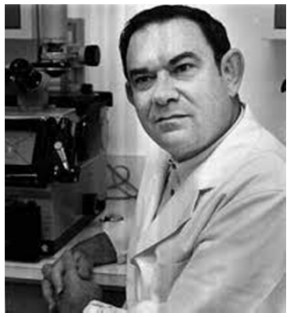
Cynthia Kenyon
Professor at UCSF

Hormone (激素) – insulin/IGF

這類問題總能勾起人們的想像力，並引發熱烈討論。加州大學舊金山分校的肯揚就說：「我們的研究顯示，動物老化的速度並非固定不變。」肯揚已鑑定出數個突變，可使線蟲的壽命大幅延長。她繼續解釋：「只要變動幾個基因，我們就能騙過死神，讓蟲蟲活蹦亂跳得更久。」只要改變線蟲對類胰島素激素發生反應的基因，就能讓牠們的壽命延長為2~6倍。若有療法能產生類似效果，或許也可延長人類壽命，肯揚猜測：「就理論上而言，若我們能活到90歲，我想不出任何理由讓我們不能活到180歲。」



青春與衰老，只有一個基因之差。最左圖是兩週大的年老線蟲，和中央兩天大的成蟲相比，顯得僵硬而遲鈍；相對的最右圖的線蟲同樣也是兩週大，卻因缺少一個感應激素訊號的基因，看起來依然年輕活躍。



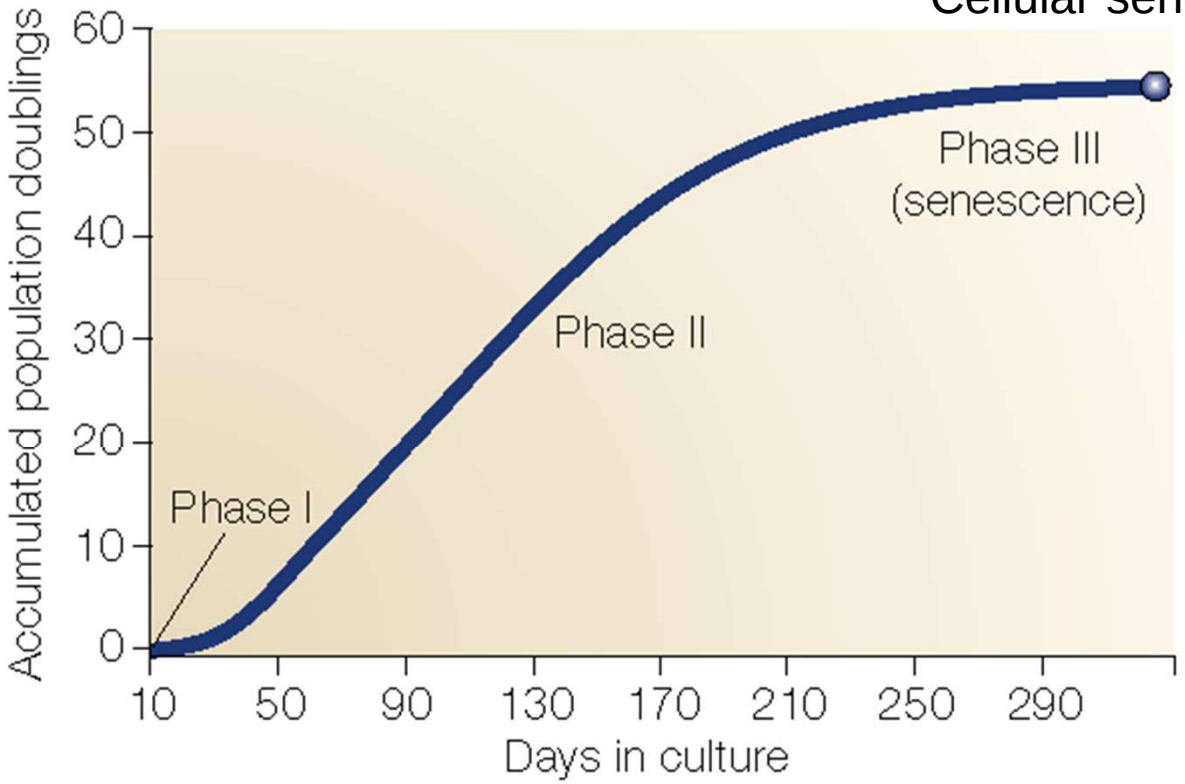
Leonard Hayflick

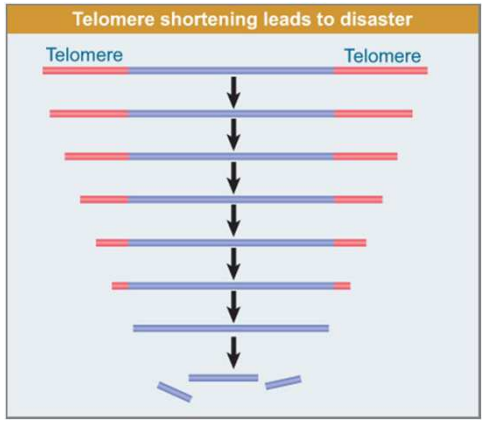
Replicative senescence (細胞複製之衰老) – telomere (端粒)

其他科學家可沒這麼樂觀。同樣任教於加州大學舊金山分校的黑弗利克說：「像這樣對基因動手腳，只是延遲老化的開始而已，到頭來還是會變老。所有東西都會變老，包括宇宙。」黑弗利克在1961年發現，培養皿中的正常人類細胞經歷特定次數（約50回）的細胞分裂後便會死亡；這上限因而稱為黑弗利克極限。黑弗利克堅持：「說什麼20年後我們都能活到200歲，根本是胡說八道。」

Hayflick's three phases of cell culture

Cellular senescence





Nature Reviews | Molecular Cell Biology

***vol.* 1**, p.**72-76 (October 2000)**

DNA上的生命計時器

telomere

現在大概人人都聽過「端粒」，也就是染色體尾端具有保護作用的一小段重複DNA序列。就連檢查護照的國境警察，在聽到肯揚入境加拿大是為了參加老化研討會時，也會脫口而出：「啊！端粒。」但端粒和老化有何關聯？

毫無疑問，端粒攸關實驗室培養細胞的存活。將結締組織中的纖維母細胞養殖在培養皿時，每次細胞分裂都會使端粒變短，端粒短到一定程度，就會通知細胞停止分裂。可重新合成端粒的酵素「端粒酶」若經活化，培養細胞就能長生不死。癌細胞能一直不斷分裂，原因之一就是端粒酶重新受到活化。

「長壽基因」的基因有許多

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

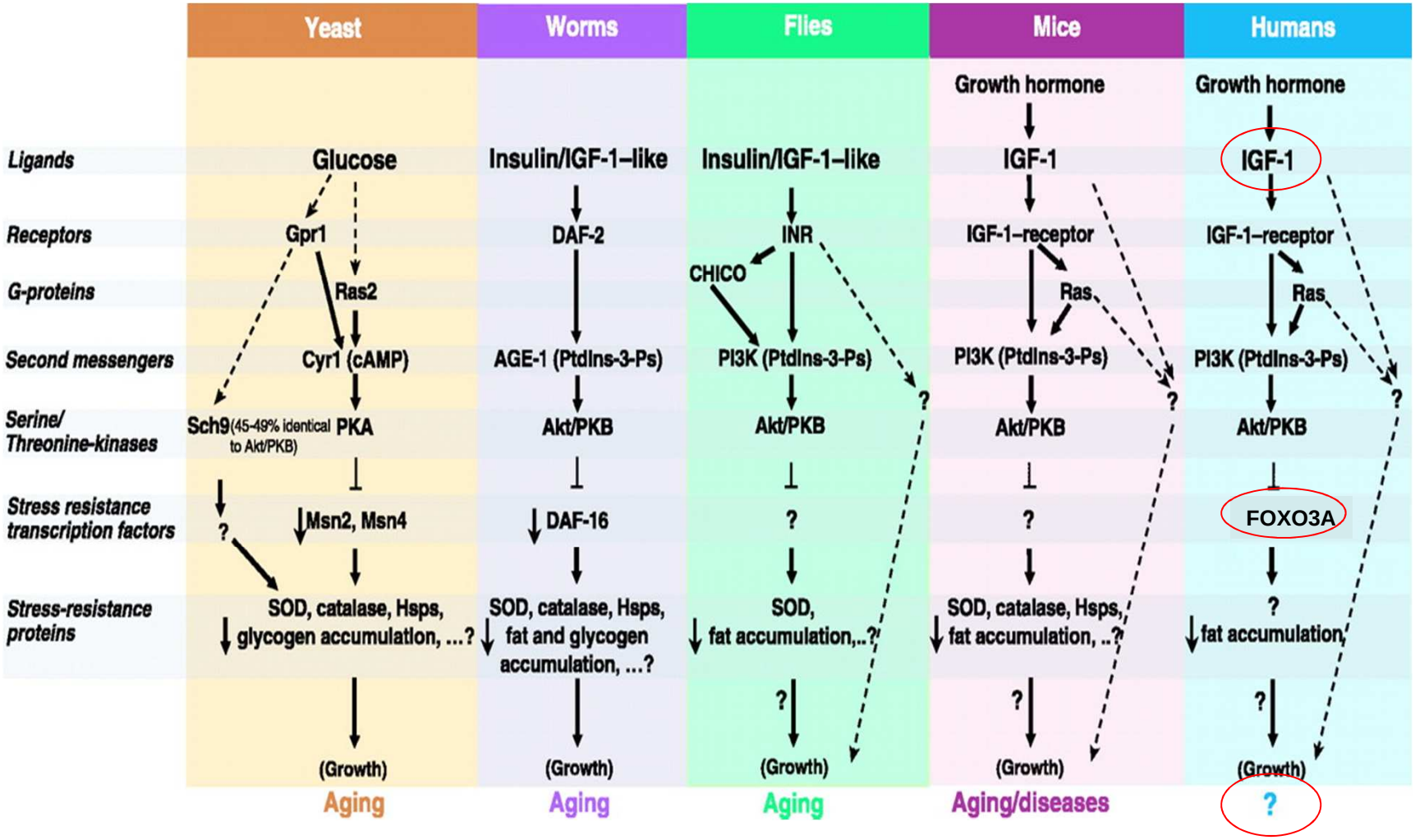
Table 5

	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)

長壽無癌侏儒村 醫界珍寶

www.chinatimes.com 更新日期:2008/08/18 04:33 *閻紀宇／綜合報導*

在南美洲厄瓜多共和國南部洛哈省一座遙遠的村落，有一百多位村民天賦異稟，他們不僅特別長壽，而且不會得糖尿病，甚至不會得癌症，被許多科學家視為研究新一代癌症療法的希望所寄。不過他們有一個「缺點」：平均身高只有一百廿分左右，是一群罹患「萊倫氏症候群」（Laron syndrome）的侏儒。

萊倫氏症候群又名「生長激素遲鈍症候群」，是一種罕見的體染色體隱性遺傳疾病，全球約只有三百多位患者，台灣也曾出現病例。主要症狀包括生長嚴重遲緩、骨質疏鬆、肌肉發育不良等。在臨床上分為兩型，第一型肇因於生長激素受體基因缺失，第二型則是「類胰島素生長因子-1」（IGF-1）出現缺失。

厄瓜多內分泌學家蓋瓦拉－阿奎爾研究萊倫氏症候群長達十多年，有了驚人發現：這些患者不會得癌症，關鍵在於他們體內的**IGF-1濃度特別低**。科學家已經證實，IGF-1濃度偏高會增加罹患乳癌、攝護腺癌、腸胃癌等多種癌症的風險。

蓋瓦拉－阿奎爾表示，醫界可以借鏡萊倫氏症候群患者的基因變異，找出降低IGF-1濃度的方法，進而達到預防癌症的功效。而且可能連第二型糖尿病也能夠預防，因為萊倫氏症候群患者向來不知糖尿病為何物。

美國南加州大學的隆格博士已經進行實驗，以基因轉殖小鼠模擬萊倫氏症候群患者的基因變異，結果發現這些小鼠的壽命是正常小鼠的十倍。隆格博士認為，降低IGF-1濃度可以減少隨著老化而來的DNA缺損，這種缺損是導致癌症的元兇之一。未來醫藥界可望以降低IGF-1濃度為目標，研發能夠預防或治療癌症的藥物。

GENETICS

Sweet longevity

Proc. Natl Acad. Sci. USA **105**, 13987–13992 (2008)

Variations in a gene that mediates responses to insulin are associated with longevity in humans, researchers have found.

Bradley Willcox of the Pacific Health Research Institute in Honolulu, Hawaii, and his colleagues looked for links between longevity and variations in five genes involved in insulin signalling and which had previously been suggested to have a link with ageing. The researchers used samples from more than 600 Japanese-American men: 213 who had lived to at least 95 years of age, and 402 who had died before the age of 81.

Variation within one of the genes, *FOXO3A*, was associated with longevity. Those with two copies of a particular version of the gene reported fewer health problems and were nearly three times more likely than those with just one copy to live to the age of 98.

NATURE|Vol 455|11 September 2008

女性較長壽， 學者找到關鍵基因。

（中央社台北13日電）北京大學教授研究發現人類兩組基因「FOXO1A」和「FOXO3A」與長壽有關，其中前者與中國女性的長壽相關，後者則沒有性別差異。學者說，長壽基因可望解開長命百歲之謎。

科技日報報導，北京大學分子醫學研究所人類群體遺傳研究室教授田小利與北京大學國家發展研究院健康老齡與發展研究中心教授曾毅聯合研究組，比較分析1000個百歲老人和1000多個年輕人的FOXO1A及FOXO3A基因，確認這兩個基因與長壽相關。

研究人員首次發現，FOXO1A基因與女性長壽相關，但與男性關係不顯著，將有助於解釋女性長壽之謎。

FOXO3A基因曾被發現與、美國、德國、等人群的長壽相關。

FOXO1A和FOXO3A是胰島素或胰島素樣生長因子介導的下游信號通路分子，與細胞週期、生長、凋亡以及血管新生等有密切關係。在代謝方面，兩者主要功能是平衡胰島素的敏感性和抗性，參與、自身免疫病以及心血管疾病，如缺血性心臟病、心肌肥大等。

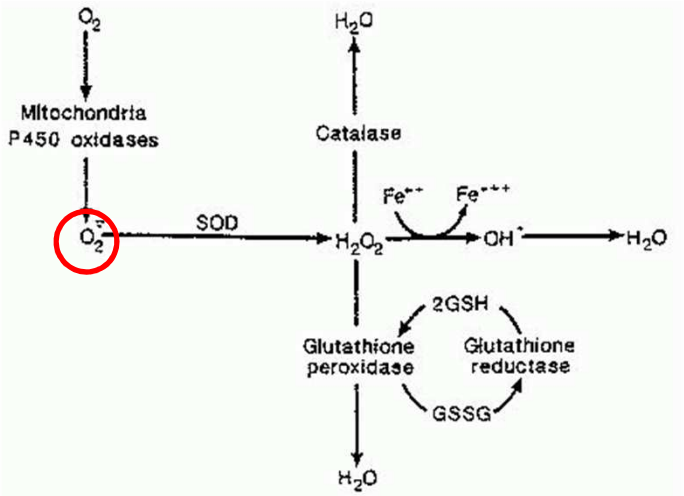
研究人員推測，FOXO3A可能透過調節胰島素抗性和長壽相關，而FOXO1A則除調節胰島素抗性外，可能透過與女性生殖系統的相互作用而影響人的壽命。99/07/13

Oxidative Damage

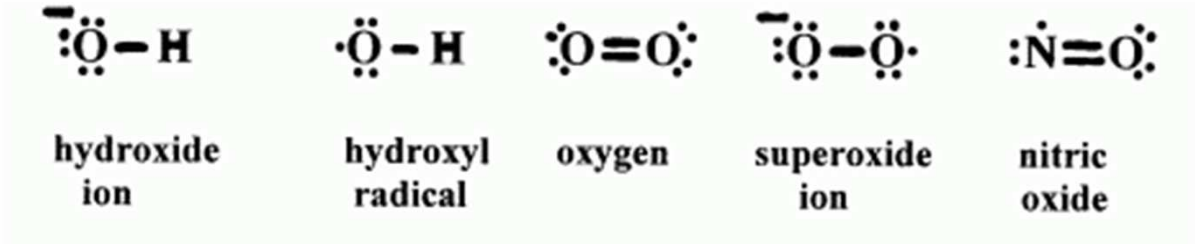
- The **free radical theory of aging** was first proposed by **Denham Harman** in November, **1954**.

Free radicals are cellular renegades; they wreak havoc by damaging DNA mitochrondria, 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



Superoxide dismutase (SOD)
超氧化物歧化酶
Catalase 過氧化氫酶



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)

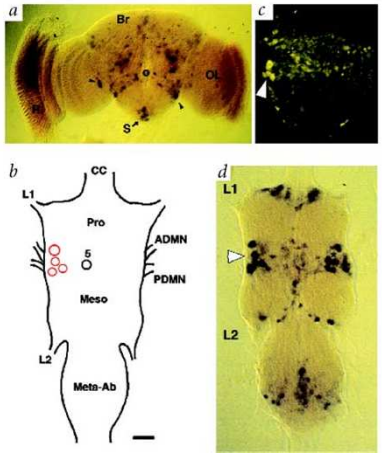


Figure 1. GAL4-activated expression of human *SOD1* in motorneurons.
Whole mounts of adult brain and ventral ganglia hybridized *in situ* with a full length dioxygenin−labelled human *SOD1* (HS) cDNA. Tissues were examined from transgenic flies bearing one copy each of HS1 and D42-GAL4 (HS1/+;GAL4/+). ***a*** , Transgenic HS expression was detected primarily in the central brain (Br), lateral margins adjacent to the lobula/lubula 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.

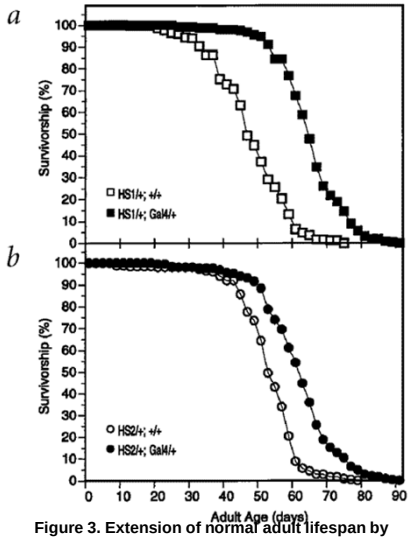


Figure 3. Extension of normal adult lifespan by expression of *SOD1* in motorneurons.
Adult $Sod^{+/+}$ males (0-24-h old) bearing a single copy of HS1 (***a***) or HS2 (***b***) and either one or no copies of D42-GAL4 were maintained at 25 °C in shell vials (10 flies per vial) containing standard cornmeal 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).

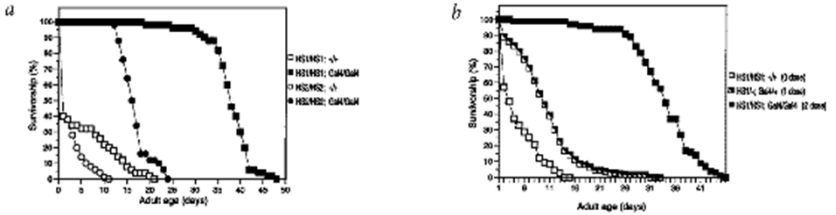


Figure 4. Restoration of adult lifespan in *Sod* null mutant by *SOD1* expression in motorneurons.
a , Adult males (0-48 h old) homozygous for *Sodx39* and also bearing different combinations of HS and D42-GAL4 transgenes were maintained at 25 °C in shell vials (10 flies per vial) containing standard 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.

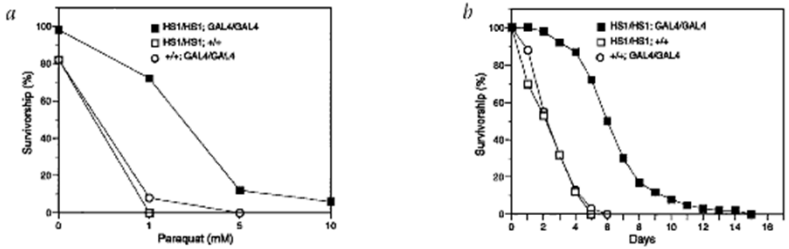
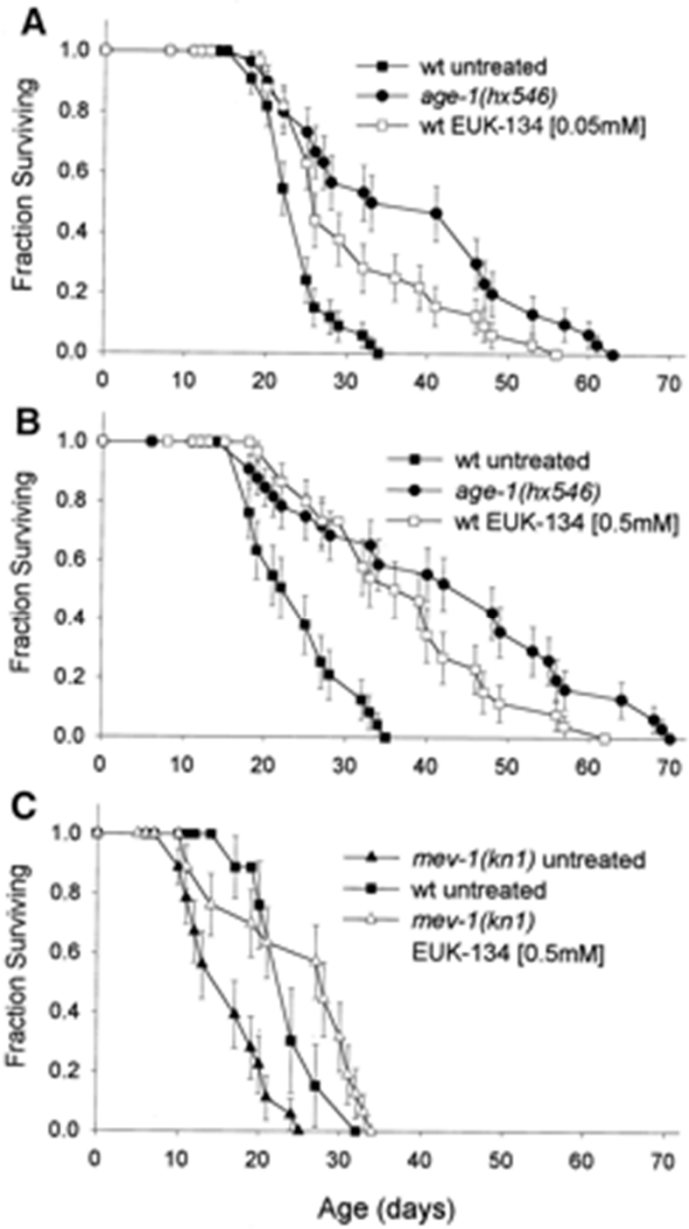


Figure 6. Expression of *SOD1* in motorneurons confers resistance to oxidative stress in *Sod* null mutants.
a , Resistance to paraquat. Adult males (0-48 h old) homozygous for Sod^{x39} and also bearing different combinations of UAS-HS and D42-GAL4 transgenes were maintained at 25 °C in shell vials 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**

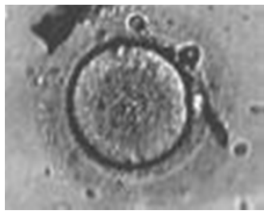
To test the oxygen radical theory of aging by the development of synthetic catalytic compounds that ameliorate oxidative stress in several disease modelsand partially rescue mice that are mutant for mitochondrial superoxide dismutase (SOD). tested the effect of two mimetics, EUK-8 and EUK-134, on life-span 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.

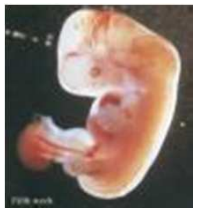
Science, Vol 289, Issue 5484, 1567-1569 , 1 September 2000

From development to aging



Fertilized egg

dividing cells



fetus

baby

toddler

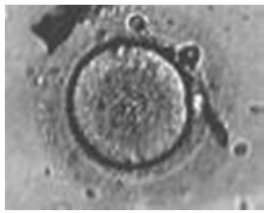
teenager

adult

elder

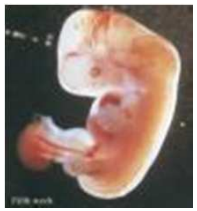
casket

From development to aging



Fertilized egg

dividing cells



fetus

baby

toddler

teenager

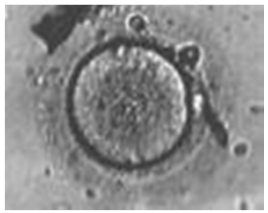
adult

elder

casket

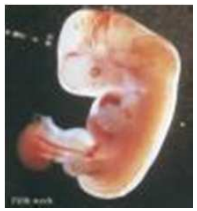
Long-lived

From development to aging



Fertilized egg

dividing cells



fetus

baby

toddler

teenager

adult

?

elder

casket

forever young?

Long-lived

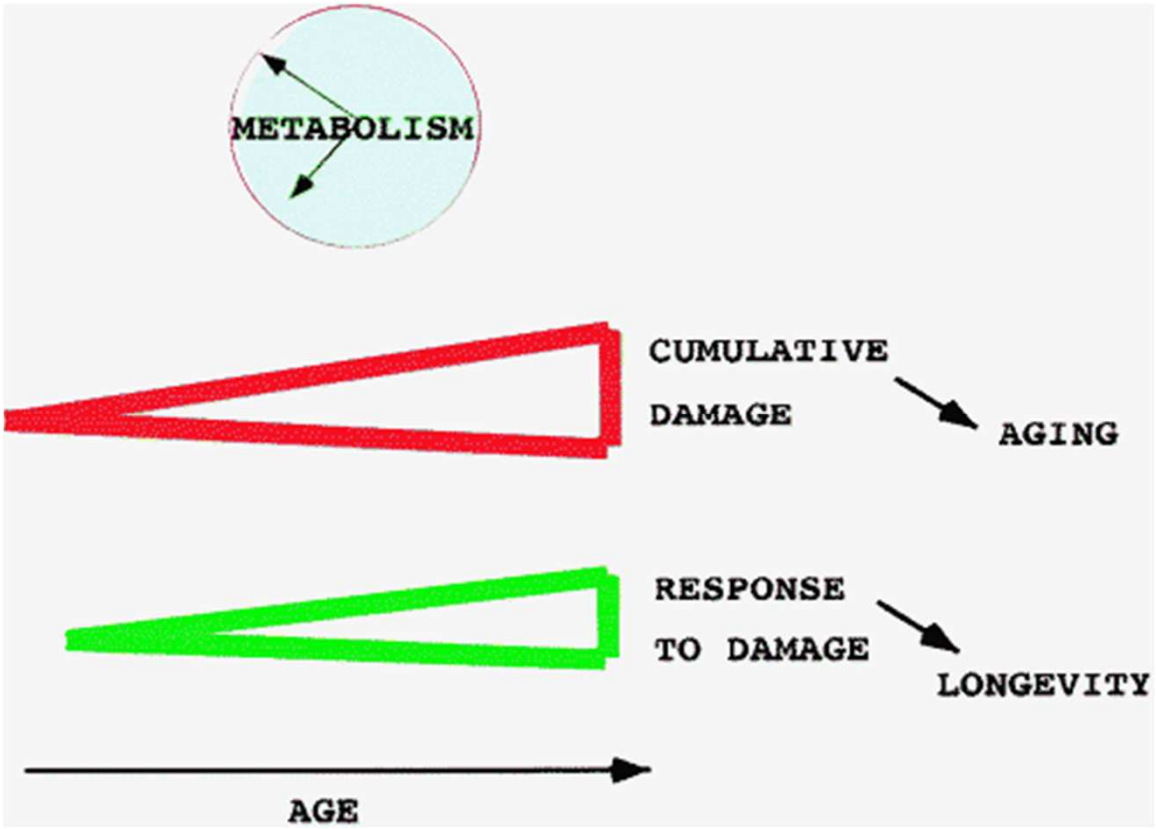


Figure 1. Life Span Is Determined by the Balance of Two Opposing Processes
Metabolism leads to the accumulation of damage (red), thus causing aging. Compensatory responses (green) limit or repair the damage, thus promoting longevity.

- 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。

延年益壽的基因作用途徑

研究長壽的科學家找到各類基因，可影響不同生物的生命長短。有些基因和*SIR2*及相關基因（統稱為Sirtuin）一樣，當有額外的基因副本，或它們所製造的蛋白質活性提高時，可延長生物的壽命；也有許多基因和其產物對壽命有負面影響效應，因此減少它們的活性可增加壽命。

以線蟲為例，胰島素和第一型類胰島素生長因子（IGF-1）的受體基因稱為*daf-2*。抑制成年線蟲*daf-2*基因的活性，會干擾胰島素和IGF-1的信號傳遞，而延長線蟲壽命多達一倍。抑制其他數個與生長相關的基因，或干擾它們所誘發的作用途徑中的分子活性，也可促進長壽。

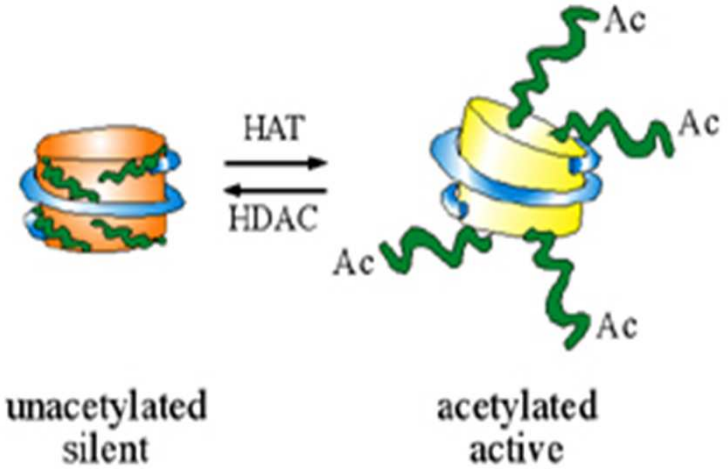
下列基因或它們的蛋白質產物，都證實在限制飲食熱量下，會受Sirtuin調節或調控Sirtuin，顯示它們也可能是老化調節中樞網絡中的一員，作者臆測Sir2和類似基因可能是這個網絡的指揮。

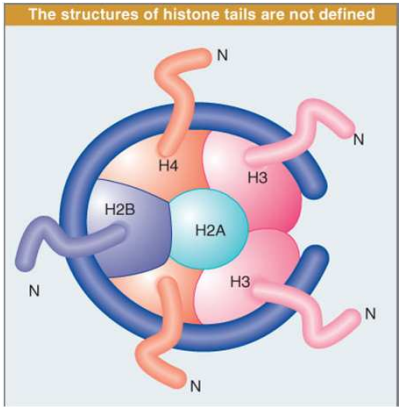
基因或作用物〔人類相對應的基因〕	生物種類/延長生命比率	增加或減少是有益	主要影響效應	操控後可能產生的副作用
SIR2〔*SIRT1*〕	酵母菌、線蟲、果蠅/30%	增加	細胞生存、代謝和壓力反應	未知
TOR〔*TOR*〕	酵母菌、果蠅、線蟲/30~250%	減少	細胞生長和感應養份	感染、癌症增加
Daf/FoxO蛋白質〔胰島素、IGF-1〕	線蟲、果蠅、小鼠/100%	減少	生長和葡萄糖代謝	侏儒症、不育症、認知力降低、組織退化
*Clock*基因〔*CoQ*基因〕	線蟲/30%	減少	輔酶的合成	未知
Amp-1〔*AMPK*〕	線蟲/10%	增加	代謝和對壓力的反應	未知
生長激素〔生長激素〕	小鼠、大鼠/7~150%	減少	體型調控	侏儒症
P66Shc〔*P66Shc*〕	小鼠/27%	減少	製造自由基	未知
Catalase〔*CAT*〕	小鼠/15%	增加	除去過氧化氫毒性	未知
Prop1, pit1〔*Pou1F1*〕	小鼠/42%	減少	腦下腺的活動	侏儒症、不育症、甲狀腺機能減退
Klotho〔*Klotho*〕	小鼠/18~31%	增加	胰島素、IGF-1和維生素D調節	胰島素抗性
Methuselah〔*CD97*〕	果蠅/35%	減少	抗壓和腦細胞傳訊	未知

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.





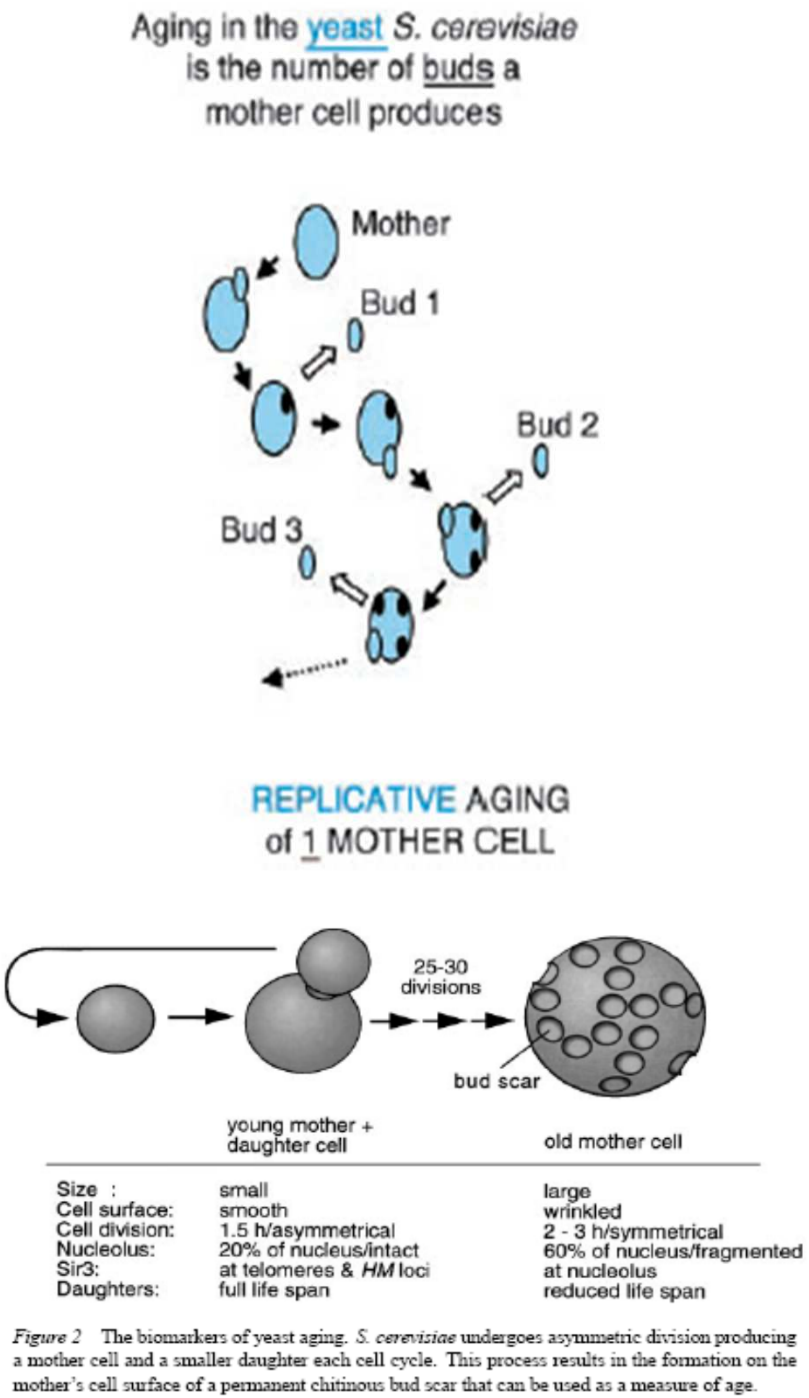


Figure 2 The biomarkers of yeast aging. *S. cerevisiae* undergoes asymmetric division producing a mother cell and a smaller daughter each cell cycle. This process results in the formation on the mother's cell surface of a permanent chitinous bud scar that can be used as a measure of age.

- **保護基因組**
- 作者會發現SIR2是一個長壽基因，最初是因為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？當時許多人認為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為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.

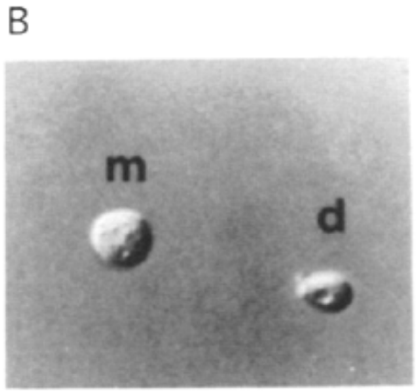
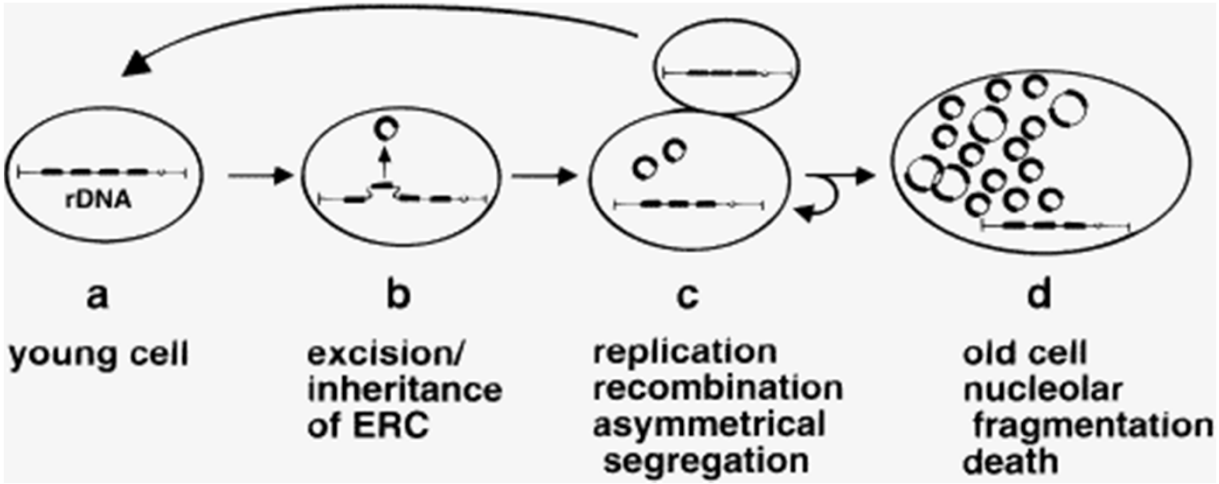


Figure 2. Symmetric and asymmetric cell divisions. All photographs were taken at 1,000x magnification using Nomarski optics. Mother cells are labeled with the letter "m" and daughters with the letter "d7 (B) A mother cell and her 42nd daughter to the right.

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



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

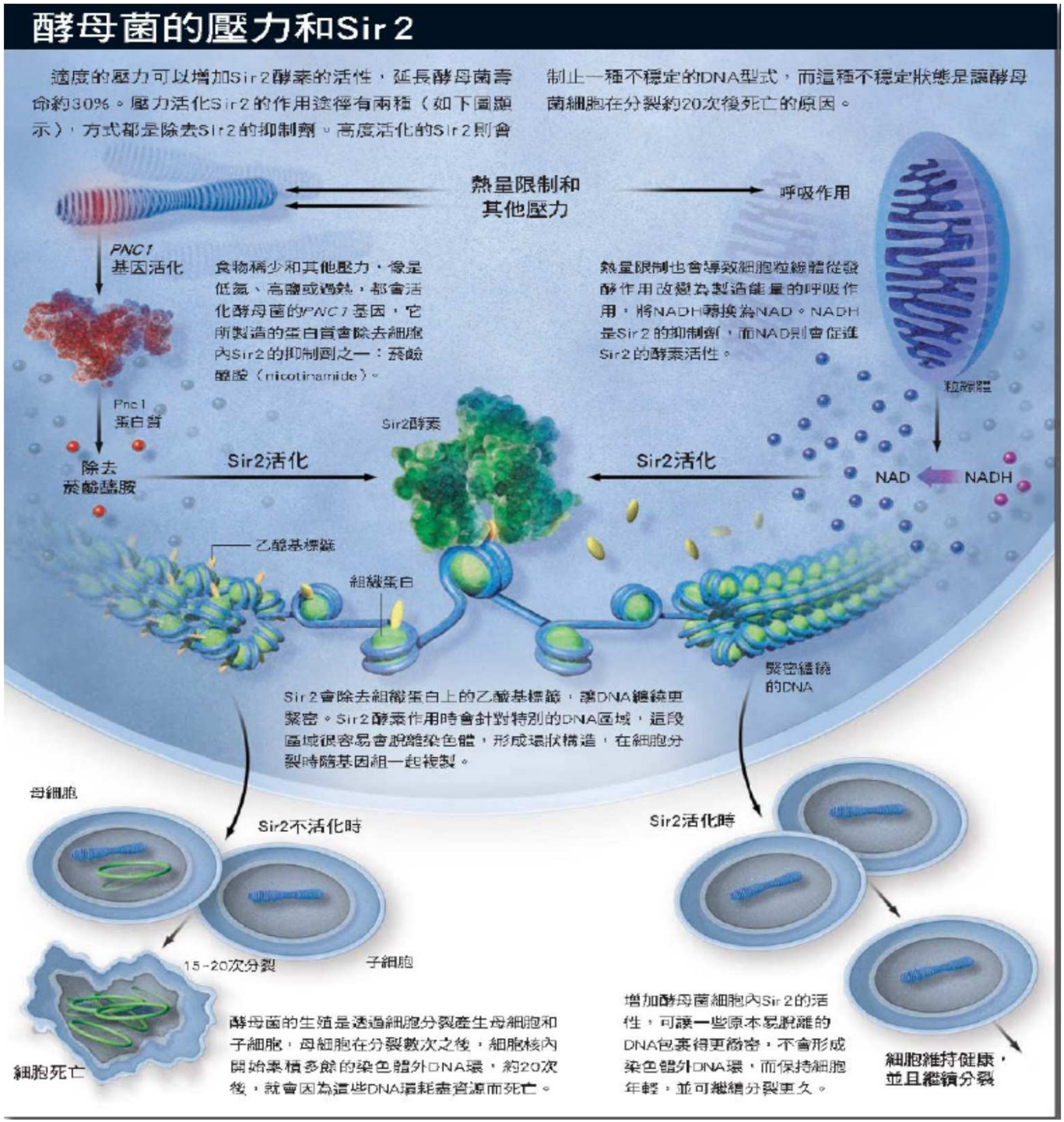
Cell, 1997, Vol 91, Pages 1033-

• 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%。這項發現可以解釋為什麼SIR2在酵母菌內可做為長壽基因。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，除了因為這兩種生物在演化上相距極遠，還因為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，因為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，因為它讓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。

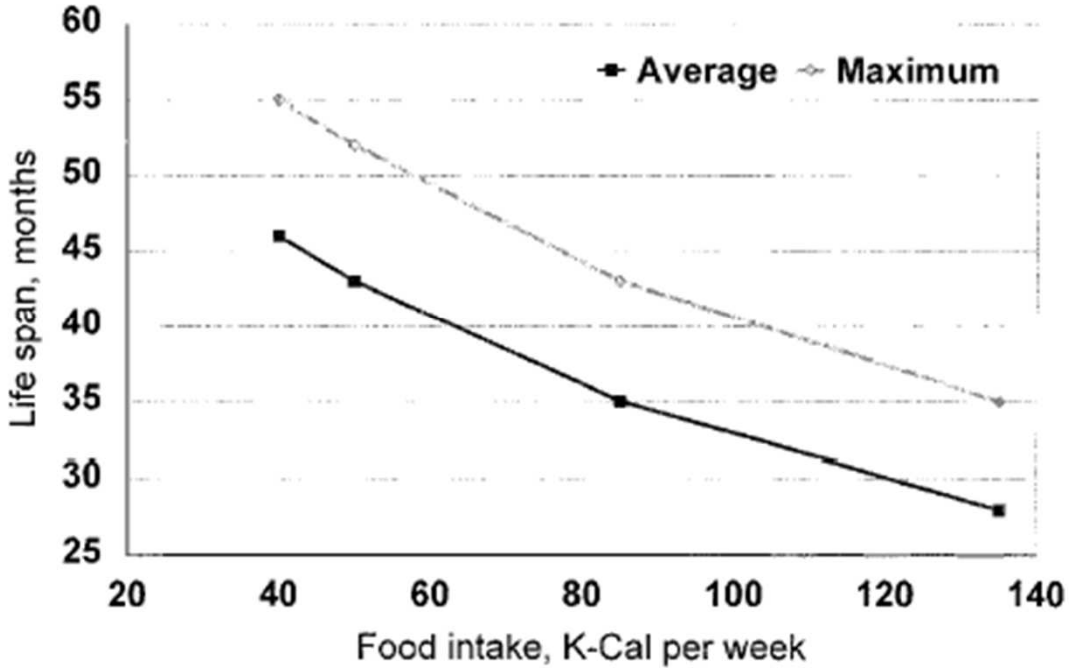
酵母菌的壓力和Sir2

適度的壓力可以增加Sir2酵素的活性，延長酵母菌壽命約30%。壓力活化Sir2的作用途徑有兩種（如下圖顯示），方式都是除去Sir2的抑制劑。高度活化的Sir2則會制止一種不穩定的DNA型式，而這種不穩定狀態是讓酵母菌細胞在分裂約20次後死亡的原因。



- 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。

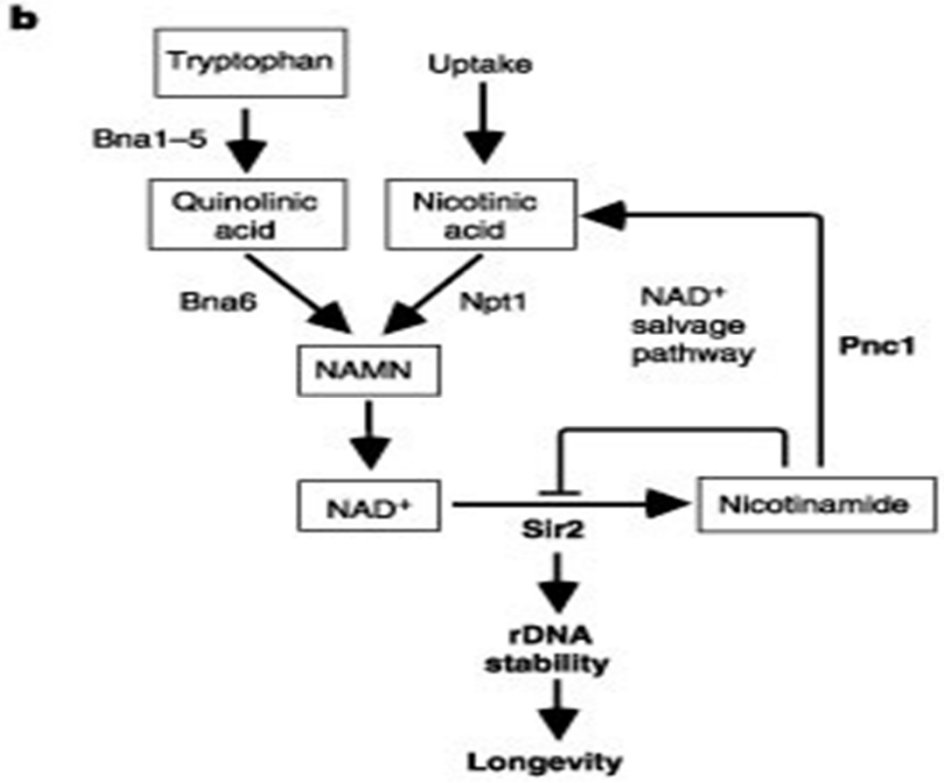
Prolong life span of mouse by reducing intake calorie



- 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，熱量限制會啟動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，正好與作者認為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轉變為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。

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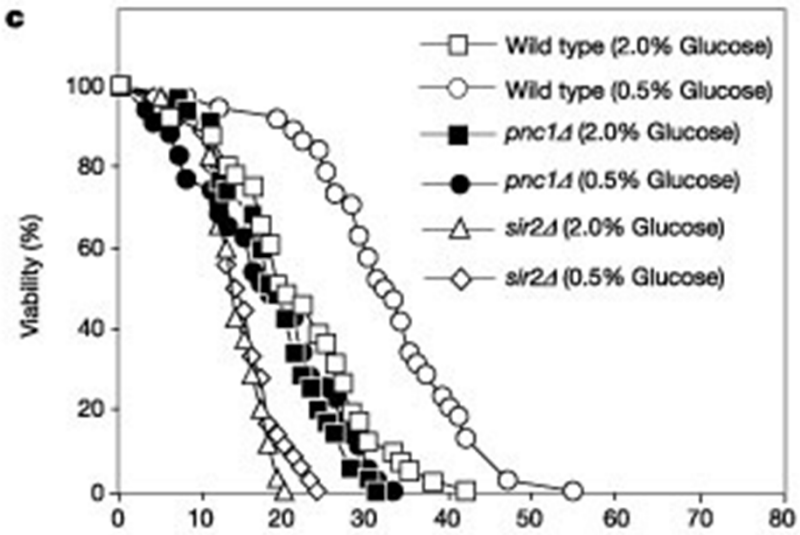
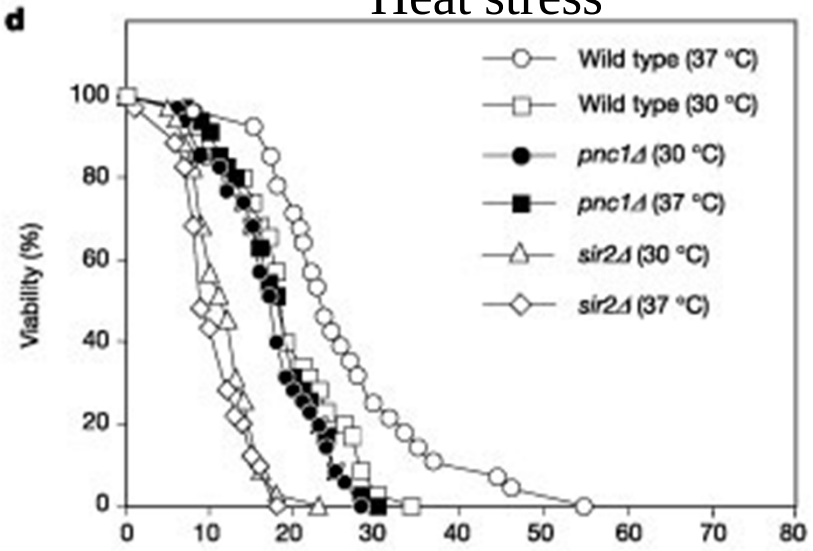
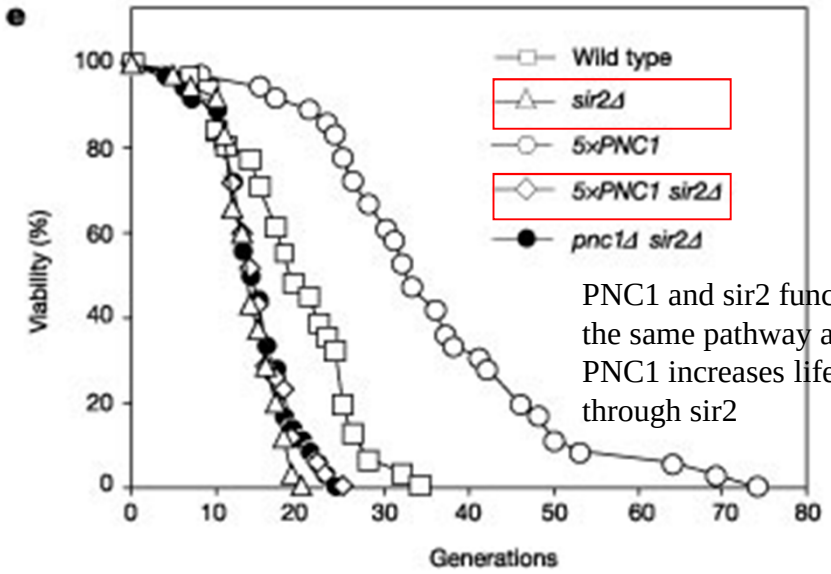


Heat stress

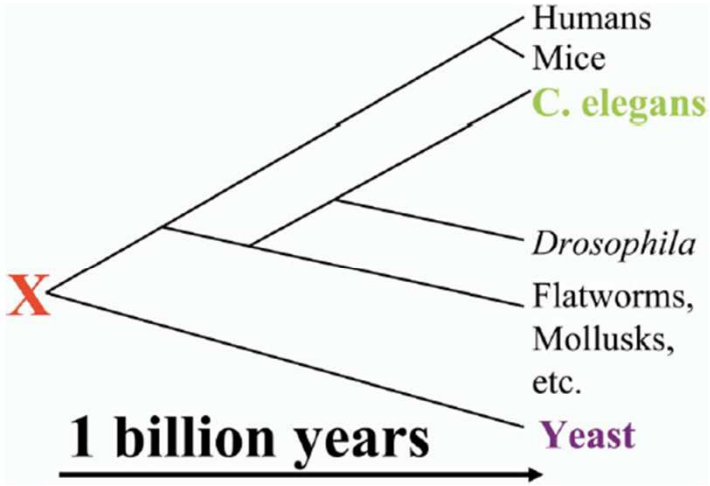


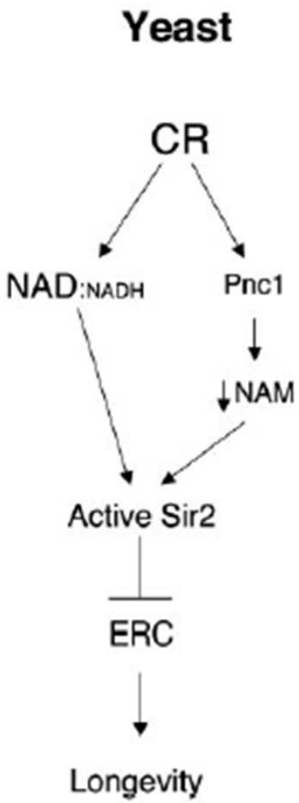
Non-stress condition

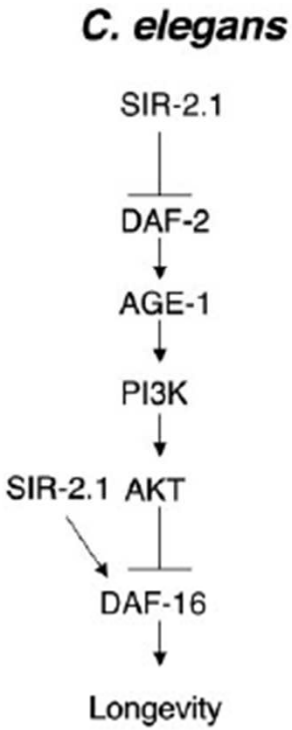


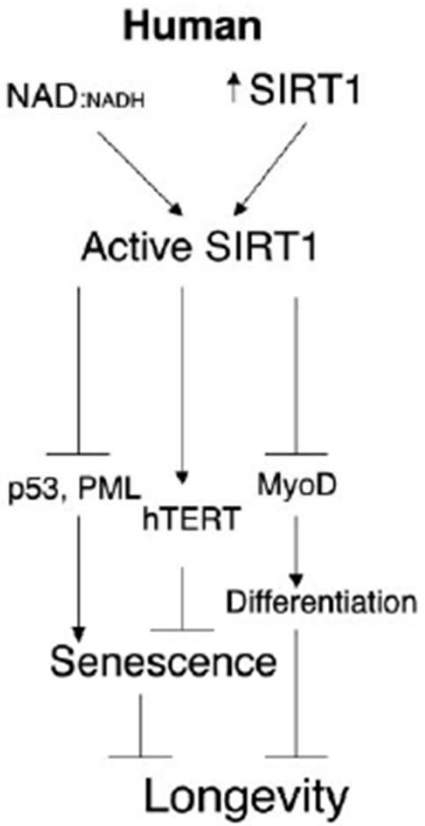
PNC1 and sir2 function in the same pathway and PNC1 increases lifespan through sir2

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.

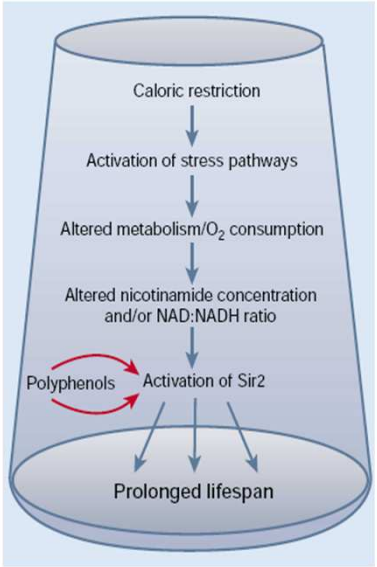


Figure 2 The pathway to long life. When yeast cells are deprived of food (caloric restriction), stress pathways are activated and the cells are forced to derive energy from alternative substrates. This produces alterations in oxygen consumption, which in turn affects the ratio of oxidized to reduced 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.

國立清華大學
National Tsing Hua University

Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan

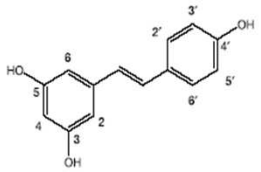
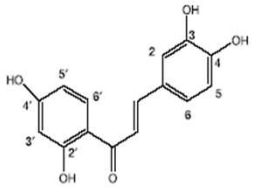
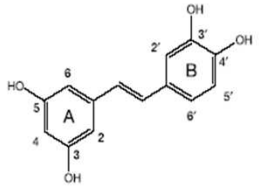
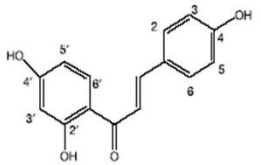
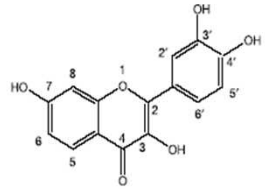
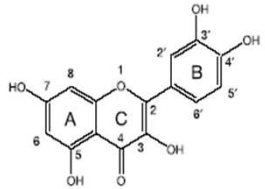
Konrad T. Howitz[1], Kevin J. Bitterman[2], Haim Y. Cohen[2], Dudley W. Lamming[2], Siva Lavu[2], Jason G. Wood[2], Robert E.Zipkin[1], Phuong Chung[1], Anne Kisielewski[1], Li-Li Zhang[1], Brandy Scherer[1] & David A. Sinclair[2]

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 ± 0.89	
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 – most in grape skin

「吃葡萄不吐葡萄皮」

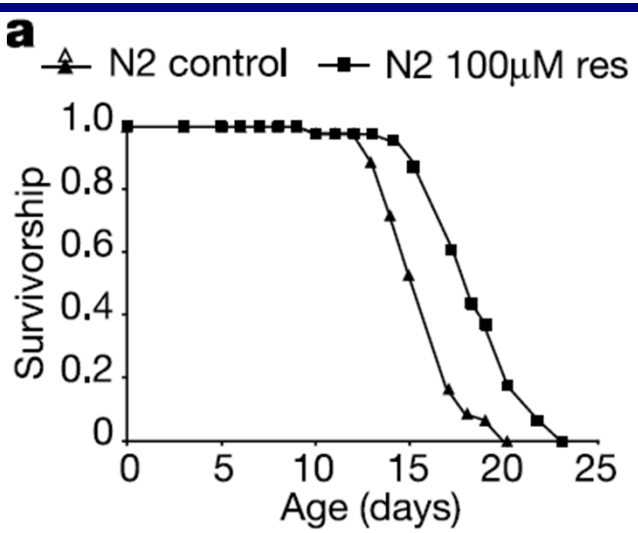
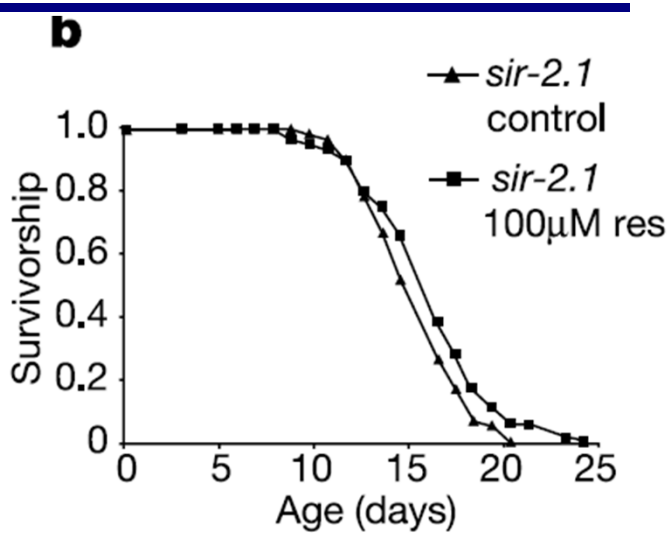
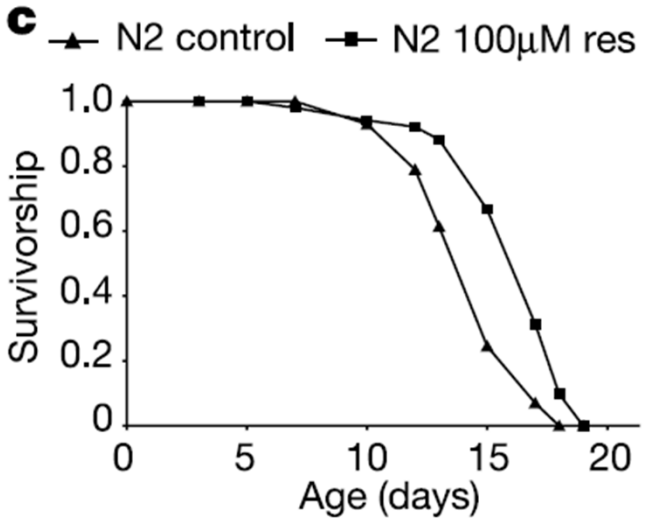
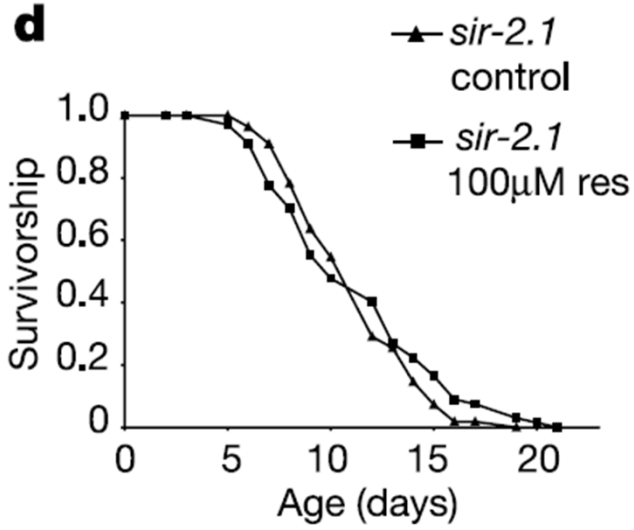
國立清華大學
National Tsing Hua University

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**

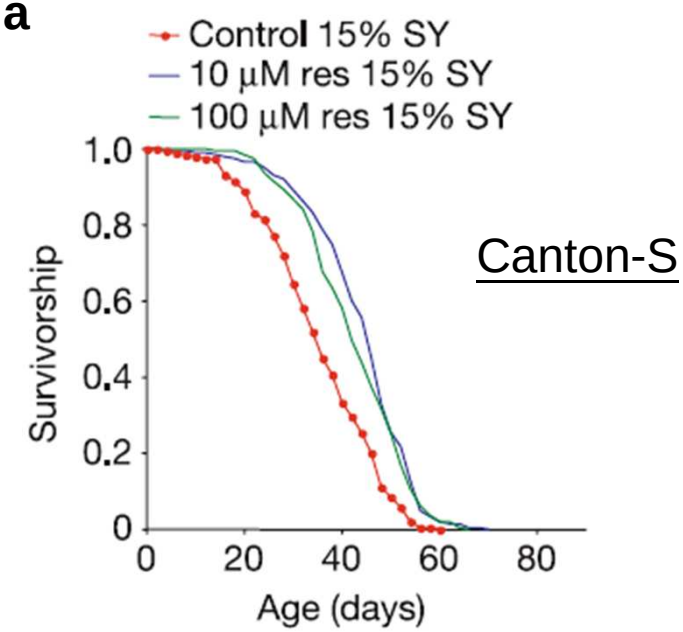
Nature. 2004;430(7000):686-9

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

	wildtype	*sir2.1* mutant
heat-killed *E. coli.*		
live *E. coli.*		

Resveratrol and other STACs extend *Drosophila* lifespan

a



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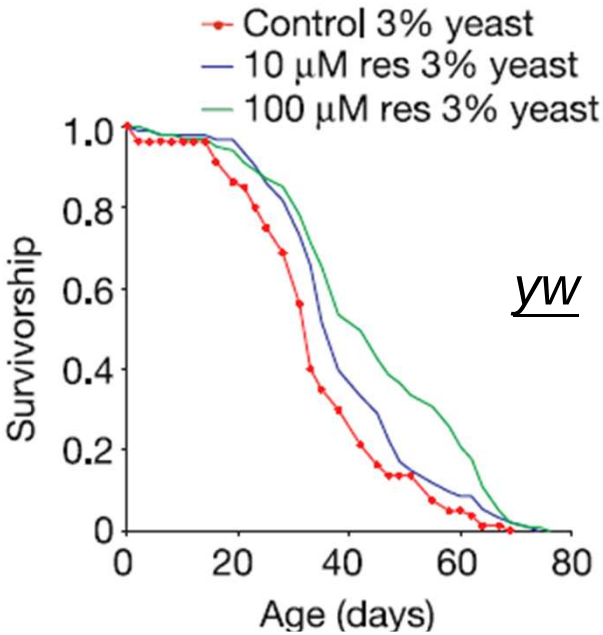

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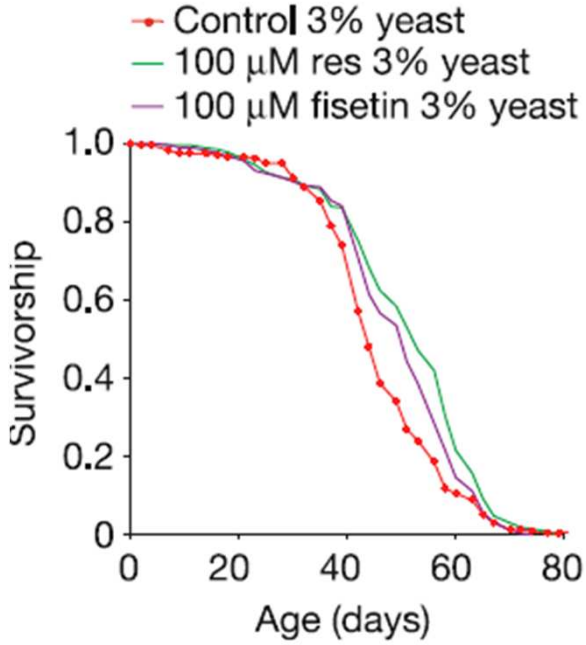

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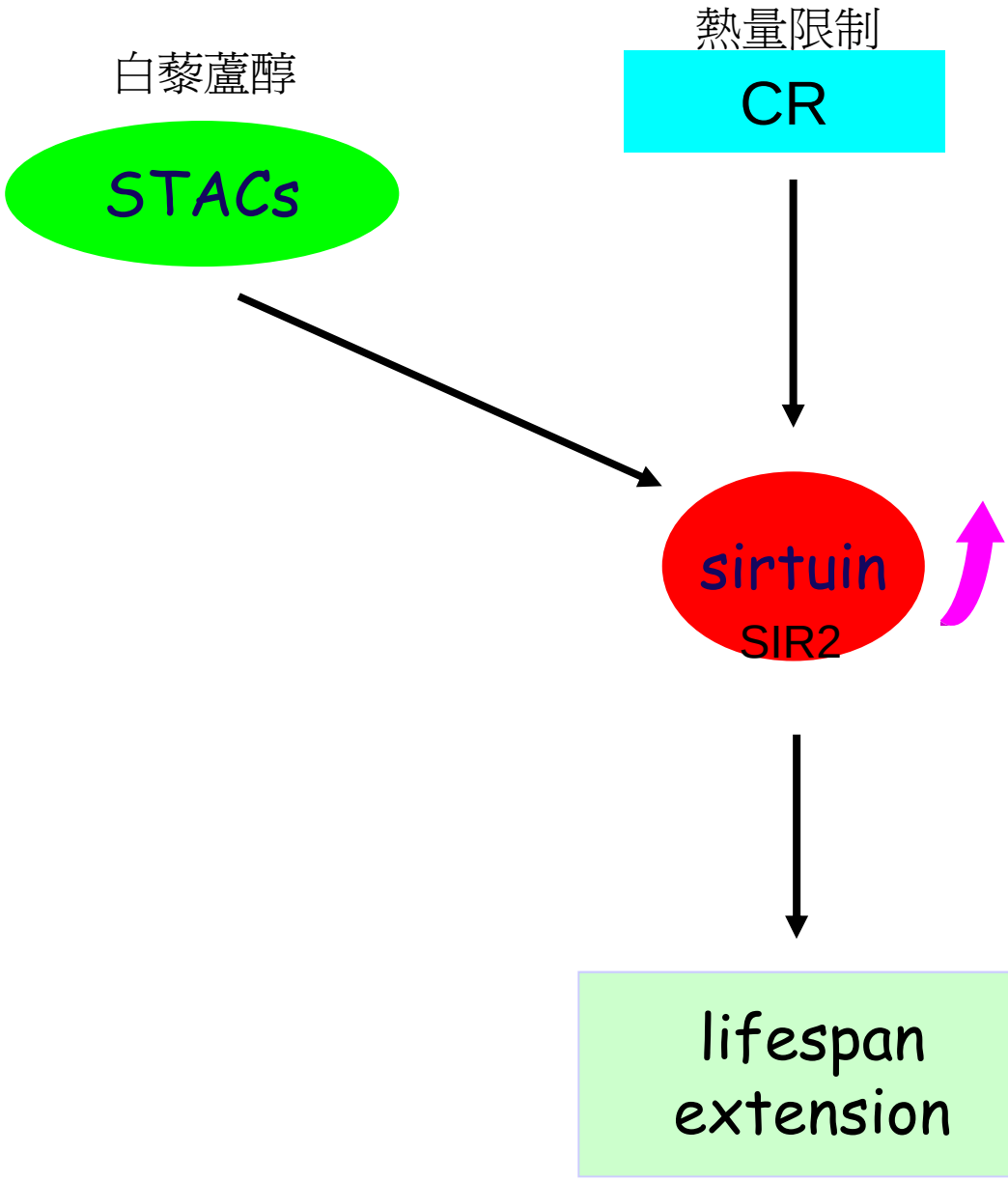
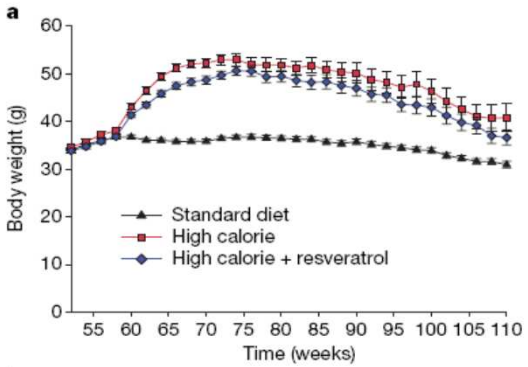

白藜蘆醇
STACs
熱量限制
CR
sirtuin
SIR2
lifespan
extension

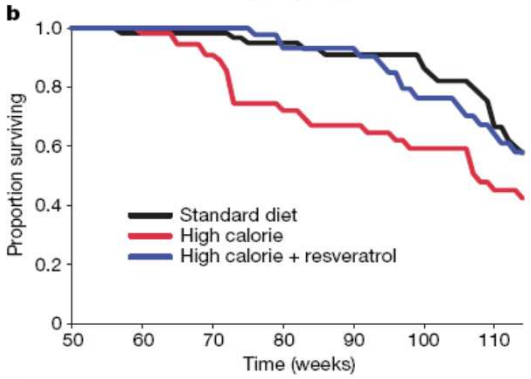
French paradox

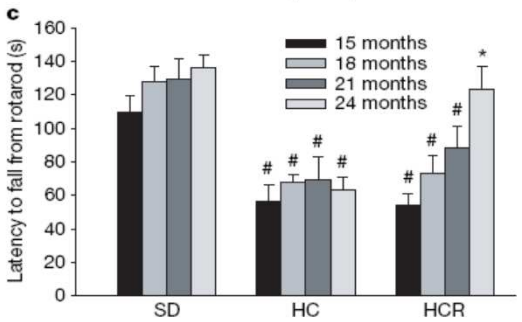
Despite a high-fat diet, people in France suffer about 40% less cardiovascular disease than expected

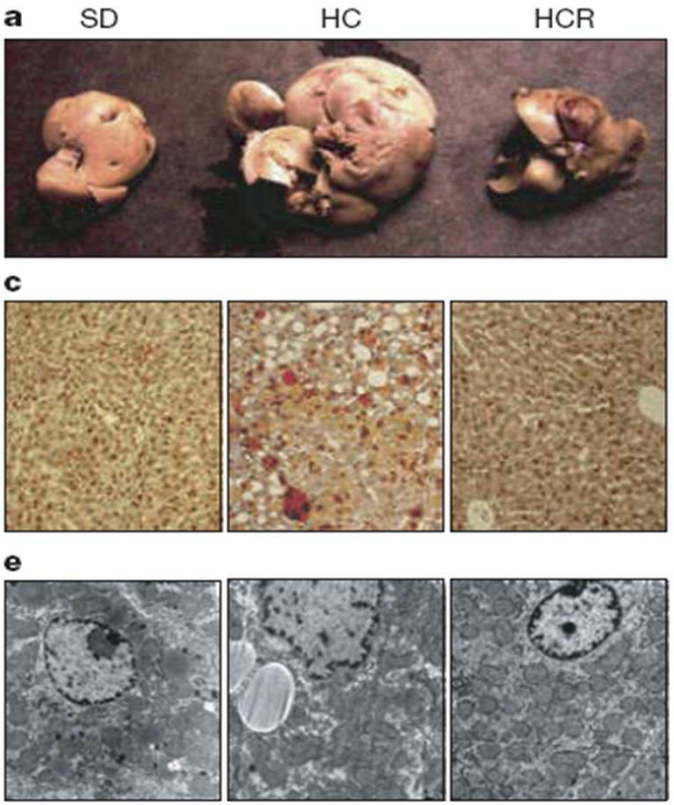
Good vintage: a compound found in red wine called resveratrol might explain why the French have fatty diets but long lives.

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

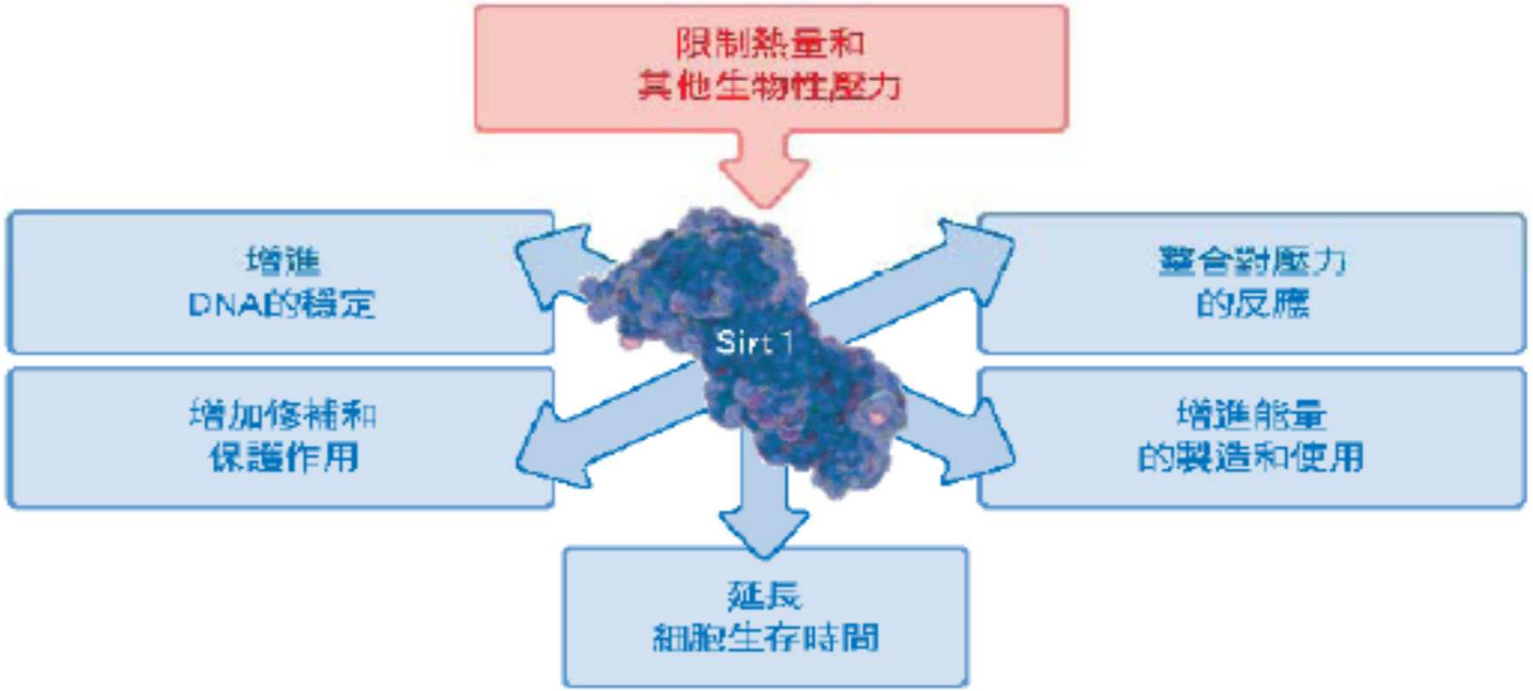








Nature **444**, 337-342 (16 November 2006)



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〉）。

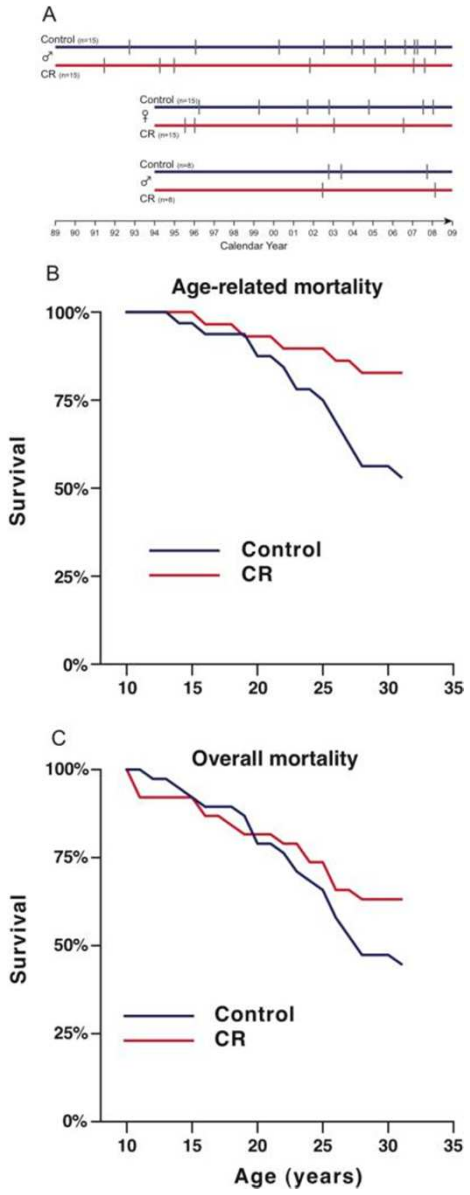
提高壽命的極限

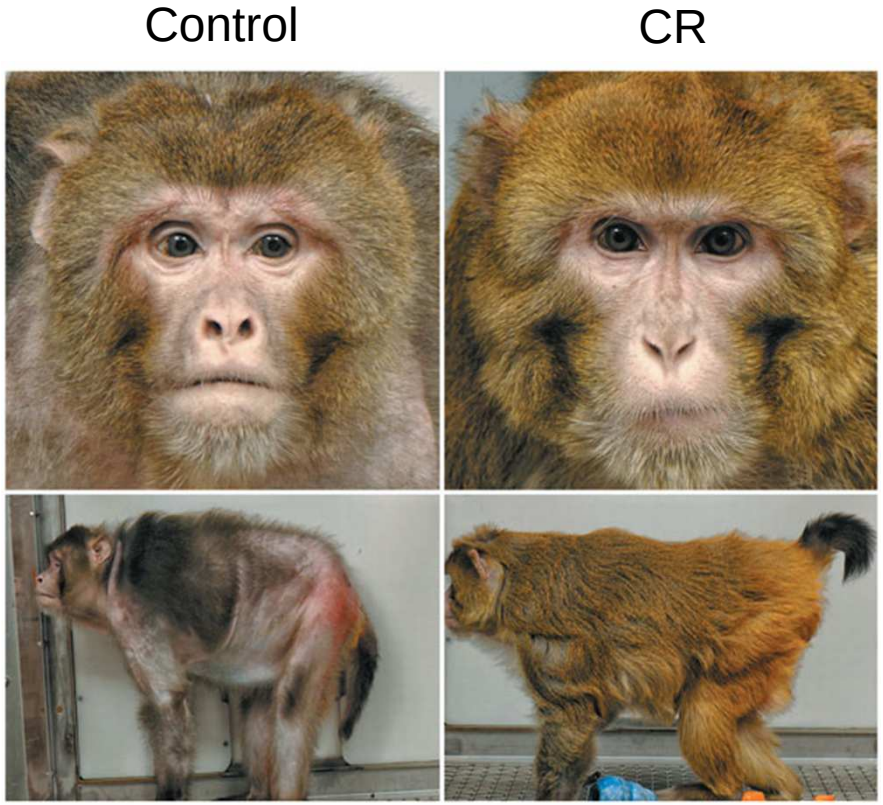
- ■負責生物因應惡劣環境變化的基因如果活躍，能夠暫時強化細胞以維持生存。
- ■因應壓力的反應長期活躍，對有些生物而言，有延長壽命、減少疾病的功效。
- ■Sirtuin是一群基因，可能是調控壓力生存機制的中樞。
- ■了解Sirtuin如何促進健康、延長壽命，可以幫助我們開發疾病療方，最終讓人類活得更久、更健康。

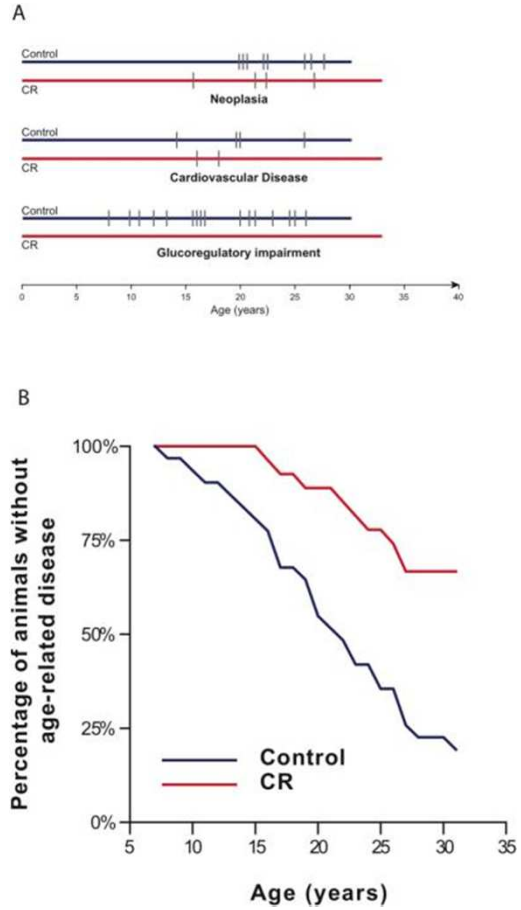
450Kcal 450Kcal 450Kcal 450Kcal

不幸的是，若想達到最佳效果，人們恐怕必須減少約30%的熱量攝取，等於是從每天的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，既可以模擬限食的生理效應，又不必強迫人們挨餓，豈不妙哉？這種我們稱之為「限食擬藥」（caloric-restriction mimetic）的東西，是否能讓人們健康得更久些，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？

Caloric restriction delays disease onset and mortality in rhesus monkeys







Science **2009**, *325,* 201

猜猜看哪一隻老鼠最老？事實上牠們全都39個月大，已經算是「鼠瑞」了。中央的兩隻看起來毛色光亮而健康，因為牠們每日攝取的熱量僅有另外兩隻齒危髮禿同伴的一半。研究者正試圖找出熱量限制影響長壽的機制。

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

CREDIT: GETTY IMAGES

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

Secrets of a long life

Centenarians now constitute the fastest-growing age group owing to advances in health care.

Nature, Vol 467|16 September 2010

台灣老化速度 世界第一

更新日期:2007/09/17 07:10 *記者:記者呂郁青／台北報導*

超級老人社會要來了，根據聯合國定義，65歲以上人口超過14%就是老化型的高齡化社會，台灣老化速度世界第一，只剩十年迎接超級老人社會，你的退休生活準備好了嗎？

根據聯合國定義，65歲以上人口占整個社會人口超過7%就是高齡化社會，當老年人口更進一步超過14%時，就遇入老化型的高齡化社會，也就是超級老人社會。

歐洲在一般人印象中是個老人化嚴重的社會，但是法國人口老化速度從7%到14%，歷經125年，瑞典花了80年，美國也花了65年，台灣卻只有24年，就進入超級老人國之林。

台灣在1993年老年人口突破7%，步入了高齡化社會，今年老年人口更突破了10%，每十個人就有一位老人，經建會預估，再十年台灣老年人口將會逼近14%，從老人國步入超級老人國，創下全球第一，台灣老化時間居於全球之冠。

台灣人口銳減的狀況嚴重，因爲生育率下降，平均壽命延長，加速台灣進入人口老年化的速度。

永保青春

「健康老化」藥丸或可成真

抗老化領域一直是西方醫藥研究的重點，專門進行抗老化研究的美國紐約「愛因斯坦醫學院」教授「巴自萊」指出，他最近研發出一種可以讓人「老得健健康康」的藥，如果順利的話，兩年之內就可以進入臨床測試階段（葉柏毅報導）

人年紀大了以後，難免病痛，除了代謝疾病與身體機能退化之外，還可能會面臨腦部退化狀況。總之，隨著老化而來的病痛，是最困擾年長者的問題。

美聯社報導，巴自萊教授原本的研究主題是抗老化，不過後來他在研究人瑞的基因時，發現一些可能可以抑制心臟病、與阿茲海默症等的體內機轉。巴自萊最初原本是要研究如何防止阿茲海默症，不過後來他發現，許多上了年紀的人，除了腦部退化疾病之外，也受代謝症候群與所苦，因此他進一步投入健康老人的基因研究，進而發現，一些蛋白(酉每)與體內基因，可能有助對抗代謝疾病、細胞死亡、發炎與壞膽固醇增加等，甚至連防範癌症，都有可能。

目前，相關研究已經得到許多國際大藥廠，像是葛蘭素史克、默克與羅氏等的高度關注，例如葛蘭素史克藥廠就開始進行一種所謂「抗老化蛋白(酉每)」，與增加體內所謂「好膽固醇」的研究開發計畫。

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