

## Recent aging discoveries



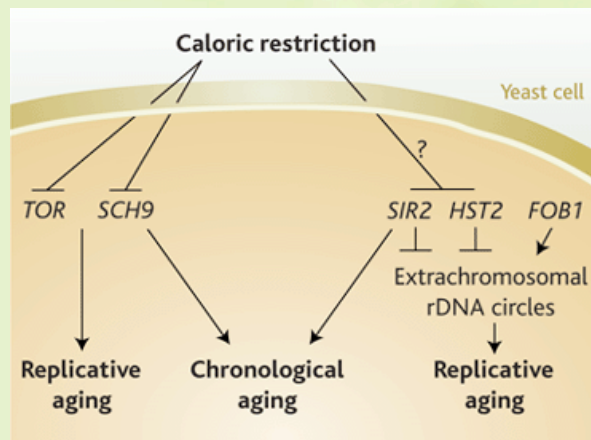
A&S300-002 Jim Lund

## Yeast aging and CR

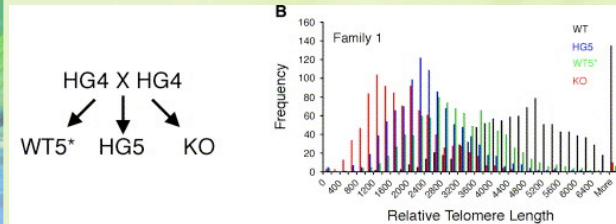
Regulation of Yeast Replicative Life Span by TOR and Sch9 in Response to Nutrients. (Kaeberlein et al., 2005)

HST2 Mediates SIR2-Independent Life-Span Extension by Calorie Restriction. (Lamming et al., 2005)

## Yeast aging and CR



## Wild type mice with short telomeres have germ cell defects



HG heterozygote telomerase RNA mutants.  
WT wild type offspring of the hets.  
KO -/- knock-out offspring of the hets.

Hao et al., 2005

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

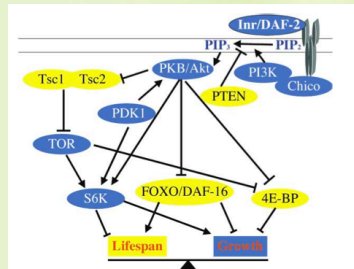


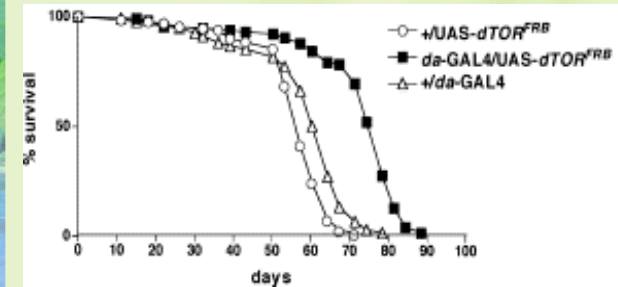
Figure S1. Signaling Pathways Balancing Growth and Lifespan. At left is the TSC-TOR signaling pathway, while on the right is the insulin/IGF-dependent PI3K-AKT pathway. Arrows represent molecular interactions based on studies in various model organisms [S6].

(Kapahi et al., 2004)

TOR=Target Of Rapamycin

(rapamycin is a product of the bacterium *Streptomyces hygroscopicus* found in a soil sample from the island Rapa Nui, better known as Easter Island!)

## Mutations in fly TOR extend lifespan



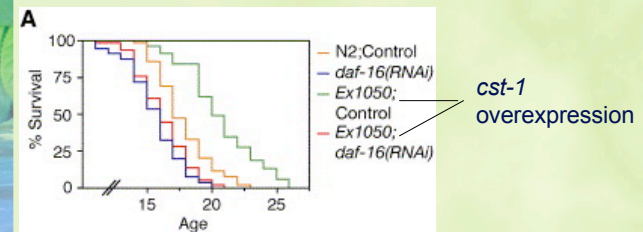
## A Conserved MST-FOXO Signaling Pathway Mediates Oxidative-Stress Responses and Extends Life Span

•Protein kinases in the Ste20(yeast)/MST (mammals)/hippo(flies)/CST(worms) regulate cellular responses to oxidative stress.

•FOXO3(mammals)/daf-16(worms) is activated by the MST kinases in response to oxidative stress.

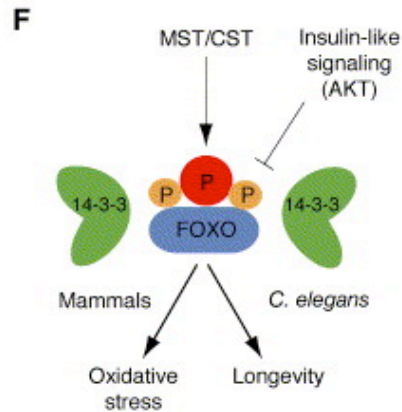
(Lehtinen et al., 2006)

## Overexpression of *cst-1* in worms extends lifespan



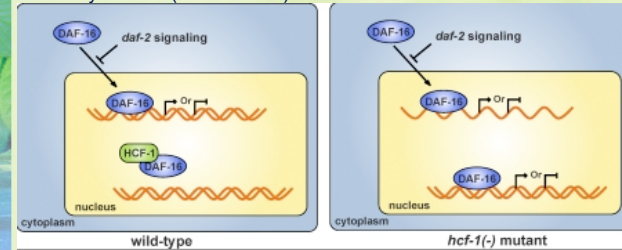
*cst-1* is a STET-20-like kinase (a signaling pathway gene)  
-This is the first study on *cst-1*, nothing else is known about it.

## MST/cst-1 signals (in part) through FOXO/*daf-16*



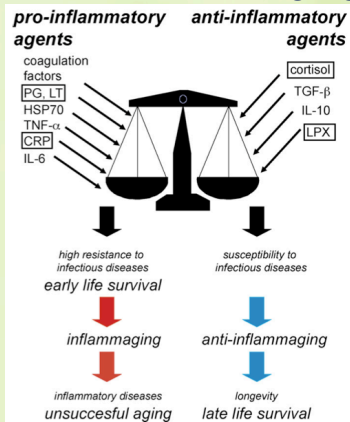
## *Caenorhabditis elegans* HCF-1 Functions in Longevity Maintenance as a DAF-16 Regulator

Ji Li, Atsushi Ebata, Yuqing Dong, Gizem Rizki, Terri Iwata, and Siu Sylvia Lee (Cornell Univ)

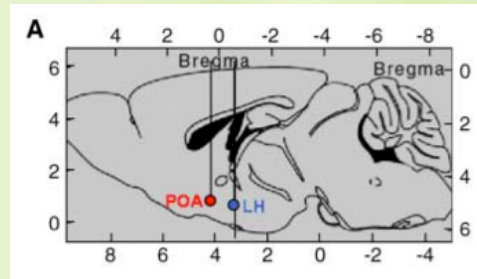


- \* *hcf-1* worms are long-lived.
- \* HCF-1 is nuclear localized and physically associated with DAF-16, and prevents DAF-16 from binding to promoters of genes.

## Growing evidence of the role of inflammation in aging



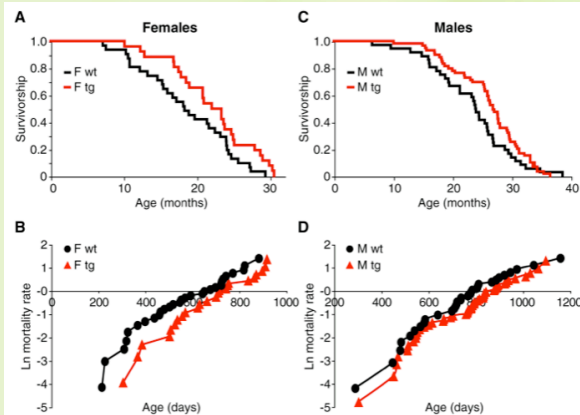
## Transgenic Mice with a Reduced Core Body Temperature Have an Increased Life Span



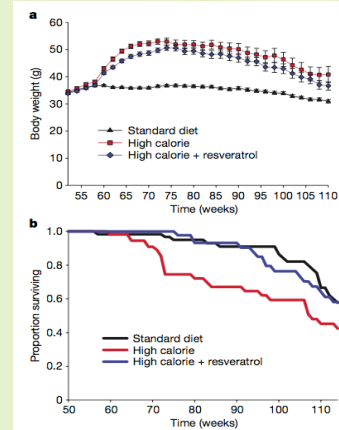
Expressed uncoupling protein UCP2 in the lateral hypothalamus.

(Conti et al., 2006)

## Reduced body temperature extends lifespan in mice

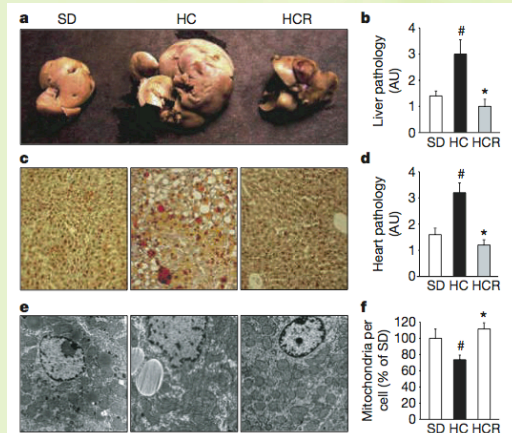


## Resveratrol improves health and survival of mice on a high-calorie diet

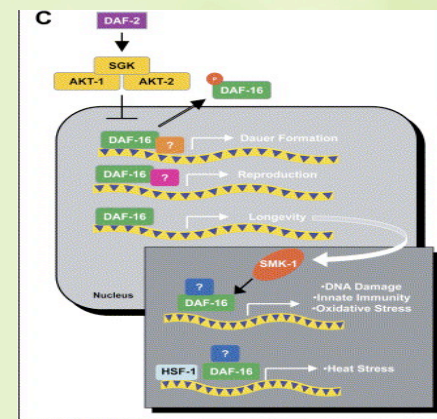


(Baur et al., 2006)

## Organ pathology improved on resveratrol



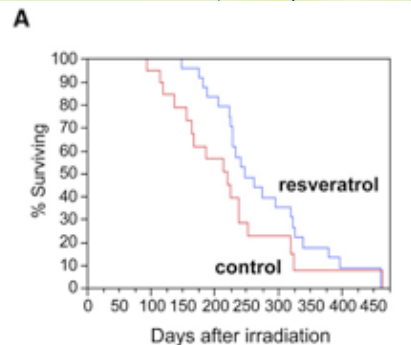
## Discoveries in the insulin-like signaling pathway





## SIRT1 Redistribution on Chromatin Promotes Genomic Stability but Alters Gene Expression during Aging.

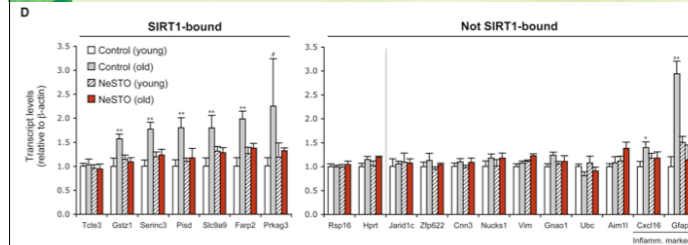
Oberdoerffer *et al.*, 2008 (Sinclair lab)



A. Survival of irradiated p53<sup>+/+</sup> mice fed normal or resveratrol-supplemented chow.

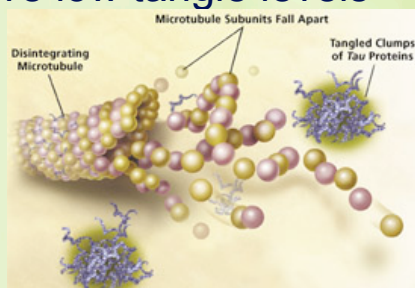
## SIRT1 Redistribution on Chromatin Promotes Genomic Stability but Alters Gene Expression during Aging.

Oberdoerffer *et al.*, 2008 (Sinclair lab)



D. q-RT-PCR analysis of SIRT1-bound genes (left) and non-SIRT1-bound genes (right) including housekeeping genes (rps16, hprt) and genes upregulated in 30-month-old mice by microarray.

## High cognitive function elderly have low tangle levels



- \* Resistant to tangle formation
- \* Tangles main component is tau protein.

Changiz Geula (Northwestern University)