Stress resistance

A&S300-002 Jim Lund

Stress resistance declines with age

- Studied experimentally in model organisms and has been observed in many different animals.
  - *S. cerevisiae* (yeast)
  - *C. elegans* (Worm)
  - *D. melanogaster* (fly)
  - *M. musclulus* (mouse)
  - *R. norvegicus* (rat)

Stress resistance declines

- Observed with several different stressors:
  - Heat stress.
  - Oxidative stress.
    - Hydrogen peroxide, high O_2, paraquat.
  - Heavy metal stress.
  - Osmotic stress.
  - Pathogen resistance.

Observed in the aging model organisms.

Stress resistance declines

How are the experiments done?

- Yeast, fly, and worm: whole animal experiments.
- Mammals: cell culture.

Observed in the aging model organisms.

Stress resistance genes

- Antioxidant proteins.
  - SOD, catalase, GSH, thioreductin
- Heat shock proteins.
  - HSPs, HSP16s, HSP70s
- Innate and acquired immunity genes.
  - Antibacterial, antifungal

Genes and conditions that activate these factors!

Resistance to high O_2 levels declines with age (fly)

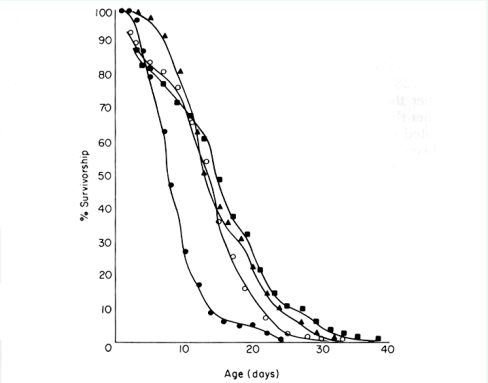
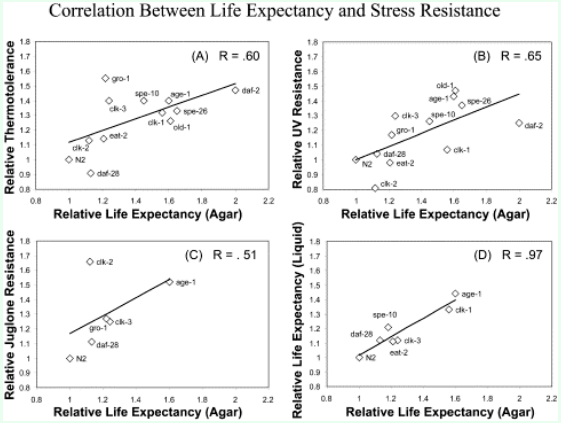


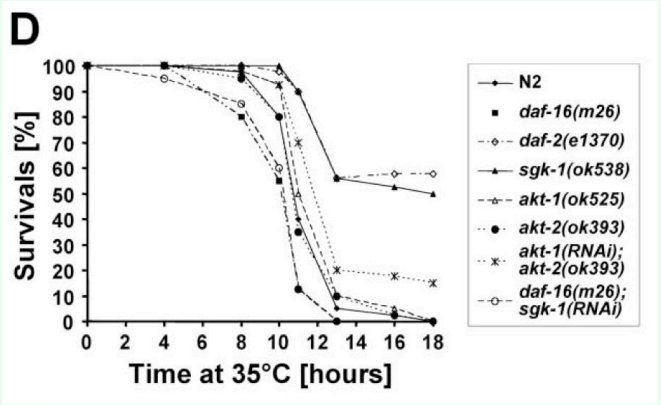
Fig. IV-9. Effect of O_2 tension on survival of *Drosophila melanogaster* [Strehler (582)]. ●, 100% O_2, N = 402; ○, 20% O_2, N = 888; ▲, 2% O_2, N = 247; ■, 1% O_2, N = 240. Remainder of gas mixture consisted of N_2.

Stress resistance and lifespan in the worm

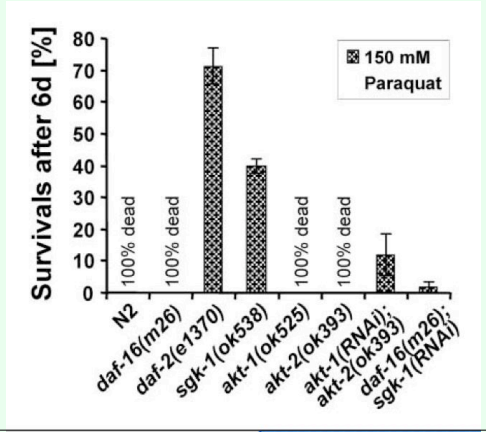


Johnson et al., 2001

Thermotolerance is increased in *C. elegans* Daf mutants



Oxidative stress resistance is increased in *C. elegans* Daf mutants

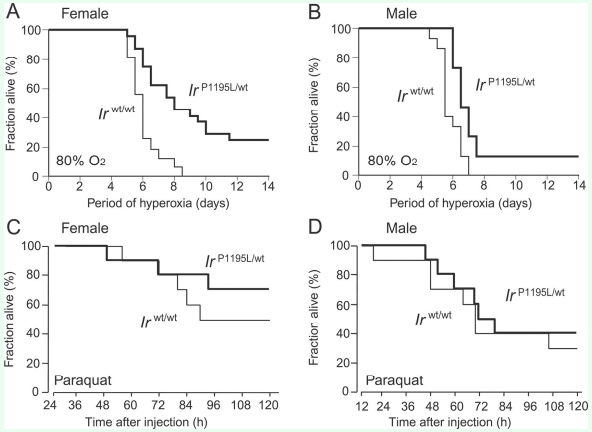


Insulin receptor KO mice

- IR knock-out, insulin receptor (*daf-2* homolog)
- (-/-) micr die diabetic ketoacidosis
- (-/+) mice normal development, suppressed kinase activity.
- Under 80% oxygen, mutant female mice survived 33.3% longer than wild-type female mice, whereas mutant male mice survived 18.2% longer than wild-type male mice.
- MnSOD activity in mutant mice was significantly upregulated.
- Additional extension of survival under oxidative conditions when their diet was restricted

Estrogen, Insulin, and Dietary Signals Cooperatively Regulate Longevity Signals to Enhance Resistance to Oxidative Stress in Mice
Baba et al., 2005. J. Biol. Chem., v280, p16417-16426.

Image



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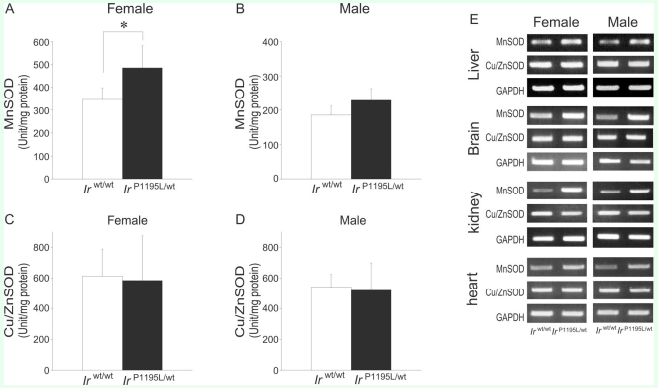

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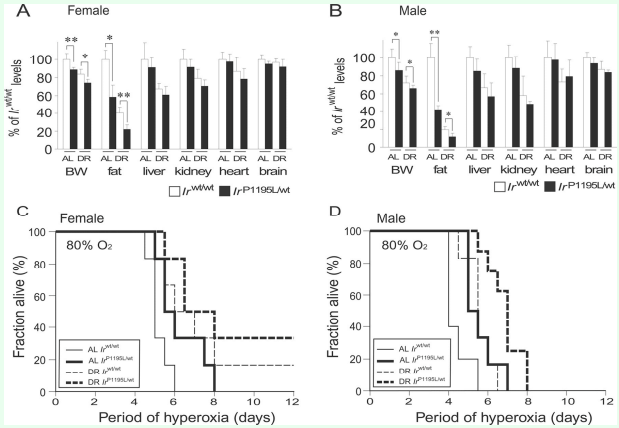
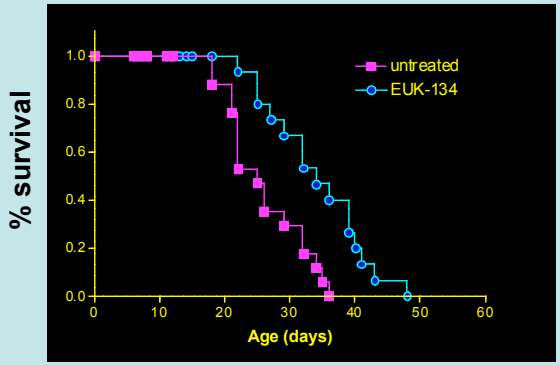


Stress resistance genes

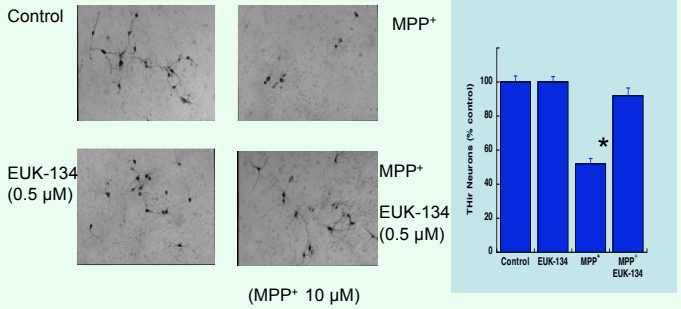
Overexpression of stress resistance genes provides stress resistance and in some cases increases longevity.

- Antioxidant proteins.
  - SOD, catalase in worm and fly.
- Heat shock proteins.
  - In worm and fly.
- Drug mimetics.

Extension of lifespan in *C.elegans* through antioxidant treatment

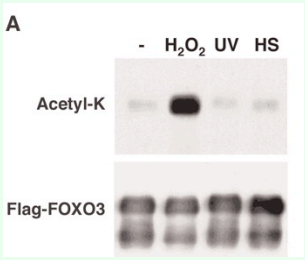


EUK-134 protects dopaminergic neurons from toxicity by MPP+



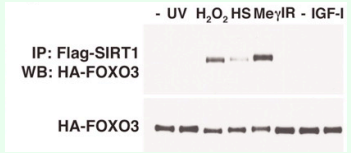
K. Pong et al., 2000 Brain Res.

Human: FOXO and SIRT1 response to stress



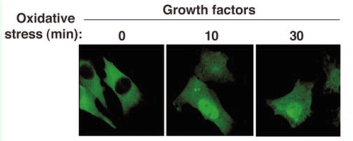
FOXO is acetylated in response to stresses.

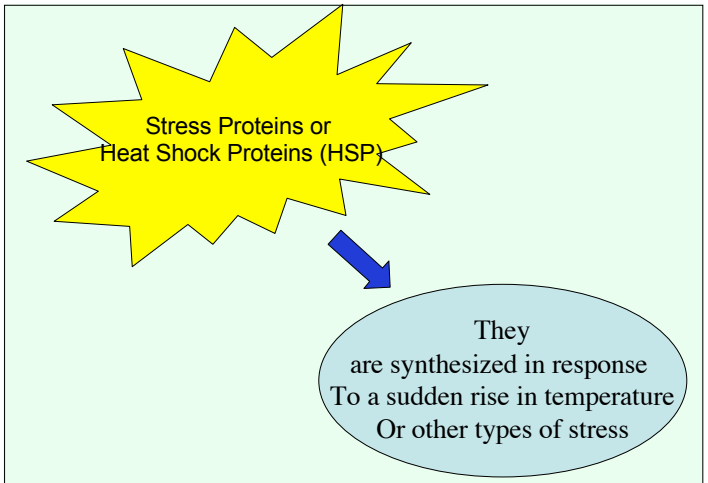
Brunet et al., 2004



FOXO binds to SIRT1 in response to stresses.

GFP::FOXO relocates to the nucleus in response to heat shock.

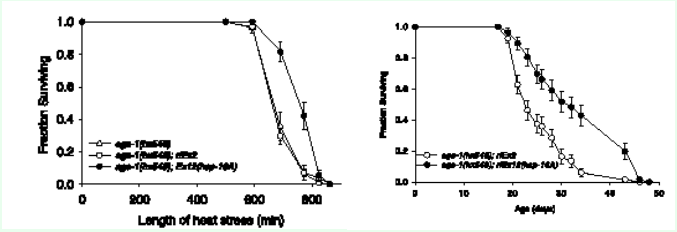




Heat shock proteins in Flies, Worms, Rodents:

- LONGEVITY is associated With stimulation (up-regulation) Of genes involved in response to stress including those of HSP
- HSPs act as chaperones and promote greater tolerance/resistance to stress (thermic and others)
- Hence, increased longevity and hormesis may depend on increased HSPs and their actions as chaperones

Extra copies of *hsp-16A* give long lifespan and resistance to heat stress



Open circle: *age-1*

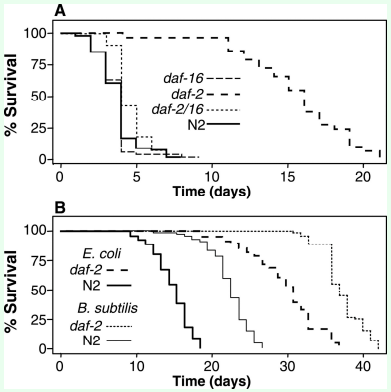
Closed circle: *age-1*;rfEx12 (*hsp-16A*)

Daf pathway also confers pathogen resistance

A.Survival on *E. faecali.*
B.Survival on *E. coli* or *B. subtilis*

Enterococcus faecalis and *Staphylococcus aureus* kill *C. elegans* by an infection-like process with remarkable overlap between the bacterial factors required for virulence in mammals and killing in nematodes.

daf-2 survival 5-fold greater on *Staphylococcus aureus*. data not shown.
Garsin et al., 2003



Stress resistance and aging

Manipulations that increase lifespan:
- Almost always increase stress resistance.
- Increase resistance to multiple stressors.
- True for many/most organisms tested.

- Insulin-like signaling pathways mutants.
- Dwarf mice.
- Caloric restriction.
- Populations selected for longevity.

Similar stress responses in yeast, worm, and fly

Gene(s)	Protein function	Life span (% increase)	Increased resistance to
S. cerevisiae (chronological life span)			
ras2Δ[a]	G-protein	100%	Oxidants, heat, starvation
↑ SOD1-SOD2[a]	Antioxidants	10–33%	Oxidants
C. elegans			
age-1[a]	PI3K	65%	Oxidants, heat, starvation
daf-2[a]	Insulin receptor-like	100%	Oxidants, heat, starvation
Drosophila			
Mth[a]	G-protein coupled rec.	35%	Oxidants, heat, starvation
↑ SOD1[a]	Antioxidant	30–40%	Oxidants
Neuronal cells (PC12)			
[a]	G-protein		Oxidants, serum withdrawal

[a]See text.

Longo et al., 1999

Increased stress resistance in long-lived populations

Organism	Population	Nature of stressor				
		ROS*	Heat	UV	Trauma	Chemical toxins
C. elegans	dauer larvae	+	+	+	?	?
C. elegans	various mutants	+	+	+	?	?
D. melanogaster	artificial selection	+	+	+	?	?
D. melanogaster	methusaleh mutant	+	+	?	?	?
M. musculus	calorie-restricted	+	+	?	+	+
M. musculus	$p66^{shc}$ mutant	+**	?	+***	?	?

*Reactive oxygen species
**Resistance to apoptosis or growth arrest of cultured embryonic fibroblasts
***Both in vitro and in vivo resistance