Mouse models of aging

Yoda (the dwarf), a four year old mouse (Photo credit: Richard Miller, U-M Medical School)

Assigned reading (PDF on class web site):
Murine Models of Life Span Extension.
Jason K.Quarrie and Karl T.Riabowol.
SAGE KE, 2004

A&S300-002 Jim Lund

Classes of long-lived mouse mutants

- Growth hormone/Insulin-like growth factor pathway
- RAS signaling mutants
- Other genes

Dwarf mice

Ames dwarf mouse

Snell dwarf mouse

- Long-lived
- Both lack GH-producing cells in the pituitary gland.

Ames dwarf mouse

- The first mammalian mutant found to have an increased average (+50%) and maximal life span (+40%).
- *Prop1* recessive mutation
  - Paired like homeodomain factor 1
- Prop1 (-/-)
  - Reduced production of thyrotropin, GH, prolactin, and gonadotropins
  - Pituitary hypoplasia

Ames dwarf mouse

- One-third normal size,
- Reduced growth rate
- Deficiencies in GH, prolactin, thyroid-stimulating hormone (TSH), and IGF-1.
- Males exhibit variable fertility, but females are infertile as a result of a lack of prolactin (treatment with prolactin restores fertility).
- Delayed reproductive maturity.

Ames dwarf mouse

Aging-related phenotypes:

- Delayed aging renal pathology
- Reduced collagen cross-links
- Delayed decline in immune function, locomotor activity, learning, and memory.
- Reduced or delayed tumor development is also observed.

CR treatment of Ames mice

- Additive: CR extends lifespan of long-lived Ames mice.

Possible mechanistic differences:

- CR reduces aging rate
  - Mortality curve slope decreased.
- Ames delays aging
  - Survival curve shifted right.

Snell dwarf mouse

- Phenotypes similar to Ames mouse.
  - Similar lifespan extension to Ames mouse.
- *Pit1* mutation
  - Pituitary specific transcription factor
- Reduced GH, prolactin, production

Snell dwarf mouse

Other aging phenotypes.

- Slower immune, joint, and connective tissue senescence.
- Snell fibroblasts are stress resistant:
  - ultraviolet (UV) light, heat, paraquat (an ROS-producing herbicide), H2O2, and the toxic metal cadmium.

Growth hormone (GH)

- GH overexpression shortens life span and is accompanied by symptoms of early aging
- Ames and Snell mice have lower GH.
- Circulating insulin concentrations also decreased
- Reduced insulin/IGF-1 signaling ->
  - Produces longevity!

Little mice

- *Ghrhr* (-/-)
  - GH-releasing hormone receptor
- release reduced, only small amounts released
- Stunted growth, 50% wild-type size
- +23 to +25% life span (only on a low-fat diet)
- Low GH -> lowered plasma IGF-1.

Laron mice

- *Ghr* (-/-)
  - GH receptor
- Normal levels of GH release but the cells can't respond to it.
- Very low IGF-1, feedback results in high GH and high prolactin.
- Plasma insulin and glucose lower.
- 50% wild-type size.
- Delayed age-related cognitive decline
- Mean (+37%) and maximum (+55%) lifespan increased.

Laron syndrome

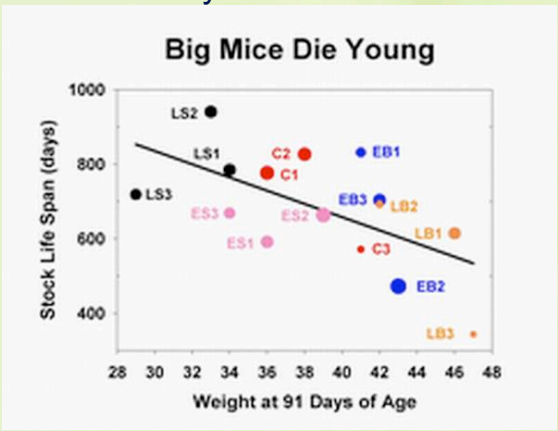
- *GHR* (-/-)
- Slightly immunodeficient.
- Stunted growth.
- Preliminary data indicates patients are possibly long-lived (small sample number).

Size vs. Lifespan

- Female mice were selectively bred from Institute for Cancer Research stock for differences in rate of body weight gain.
- Mice were selected for differential rates of growth either early (0–10 days) or later (26–56 days) in the first 2 months of life.
- Low body size well correlated with longer life span.

Miller at al., 2000

Plot of life span vs size for 15 Atchley mouse stocks



P66shc (-/-) mice

- One of 3 alternate splice forms of *shc*
- *shc* binds SOS (a guanine nucleotide exchange factor) upon tyrosine phosphorylation
  - Part of IGF and Ras signaling pathways.
- Involved in apoptosis and stress response pathways.
- Cell lines from p66shc mice are resistant to UV and oxidative stress.
- Wild-type size! And development and fertility.
- Don't develop atherosclerosis on a high-fat diet.
- +30% lifespan.

Ras signaling and aging

- Ras/MAP kinase (MAPK) signaling pathway

Receptor tyrosine kinase (RTK)
↓
GTPases (Ras)
↓
MAPKKK
↓
MAPKK
↓
MAP kinase
↓
Cellular response

Ras signaling and aging

- Shc activates the receptor tyrosine kinase (RTK) thus activating Ras/MAPK signaling.
- Oxidative stress induces the Ras/MAPK pathway.
  - UV, hydrogen peroxide, paraquat.
- Manipulations that induce Ras/MAPK increase oxidative stress resistance in cell culture (Guyton et al., 1996l Wang etal., 1998).

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Ras signaling and aging

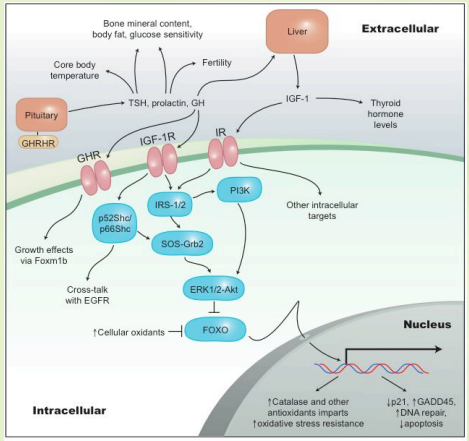
- Genes activated by Ras signaling have reduced expression levels in senescent cells.
  - *In vitro* senescence models.
- Ras/MAPK signaling reduced in late passage fibroblast cells.
- Reduced activation of the Ras/MAPK pathway also observed in aging T-cells.
- Caloric restriction attenuates reduction of Ras/MAPK signaling!

Igf1 knock-out mice

- The single knock-out Igf1r+/- mice lived an average of 26% longer than wild-type mice.
- Female Igf1r+/- mice lived an average of 33% longer than wild-type,
- Male Igf1r+/- mice lived an average of 16% longer.

Insulin receptor (*Insr*) loss

- Shortened lifespan in mice and humans
- Targeted knockout in adipose tissue produces 18% lifespan extension.
  - Cre-loxP used for the tissue specific knockout.
- Lower body fat observed, food consumption and metabolism normal.

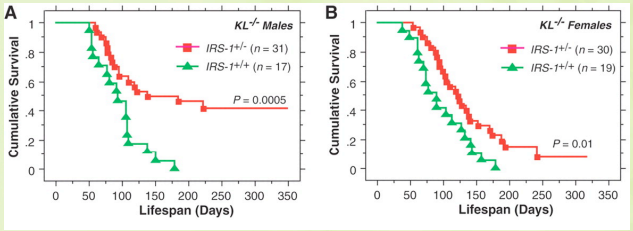


Physiology and biochemistry of the GH/IGF-1 axis
Quarrie and Riabowol , 2004

Klotho

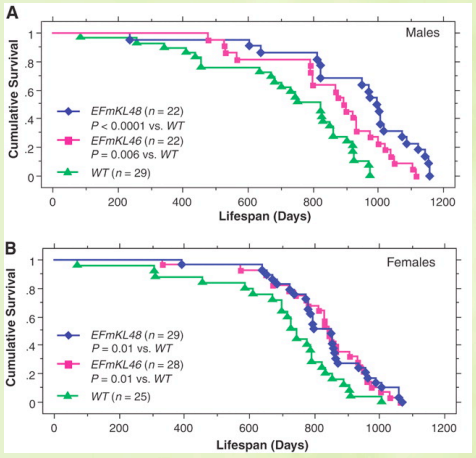
- First identifed as a hypomorphic mutation that reduced lifespan, shows accelerated aging. (*KL* (-/-))
- Klotho overexpression extends lifespan.
  - +20-31% males, +20% females
- Transmembrane protein with a cleaved extracellular domain that has ß-glucosidase activity.
- Inhibits insulin and IGF1 signaling!

Reduced insulin signaling rescues aging phenotypes of *KL (-/-)* mice

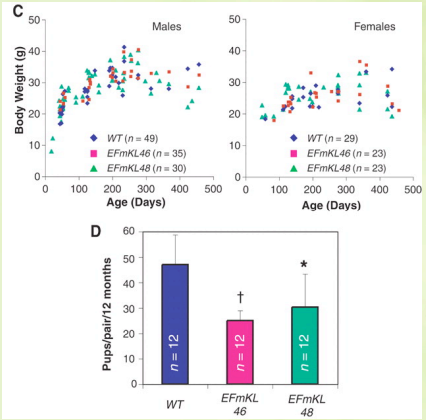


KL (-/-) combined with IRS-1 (-/+) rescues short KL (-/-) lifespan. IRS-1 is part of the insulin-like signaling pathway. (Kurosu et al., 2005)

Klotho overexpression extends lifespan



Klotho mice aren't caloric restricted but have reduced fertility



Other genes that affect mouse lifespan

- Thioredoxin overexpression.
  - Anti-oxidant gene, provides electrons for peroxiredoxin.
  - Extends lifespan 22-35%
- Peroxiredoxin (-/-)
  - Free radical scavenging enzyme
  - Short lifepspan, develop anemia and cancer at 9 months.
- DNA repair mutations reduce lifespan
  - p53 mutations, XPD TTD (5'->3' helicase), *Wrn* (DNA helicase).