Species differences:
The dark matter of longevity genetics

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Poster references:

Searching under lampposts:

Mainstream genetics of ageing and longevity studies polymorphisms within species, such as alleles of apolipoprotein E (*APOE*) in humans; and evolutionarily conserved, nutrient sensing, metabolic fine-tuning pathways such as insulin like signaling (ILS) and target of rapamycin (TOR), involved in things such as the caloric restriction (CR) response in model organisms (Steele, 2020).

The problem:

A calorically restricted mouse lives 4 or 5 years, not decades like a naked mole rat or elephant, nor centuries like a bowhead whale or ocean quahog. Evolutionarily conserved genes are unlikely to cause many differences between species. Genes for species differences are hard to study: you can't breed a mouse with a whale, or easily keep a whale in the lab (Bahry, 2022*a*).

The question:

How do long lived species live so much longer than short lived species? How do they resist cancer and protein misfolding? Do we already use the same longevity tricks, or do they have any novel ones to someday apply to ourselves?

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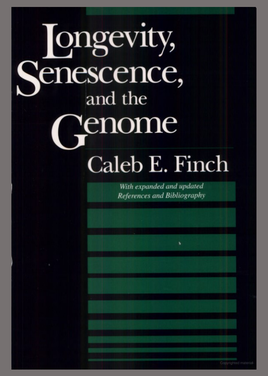
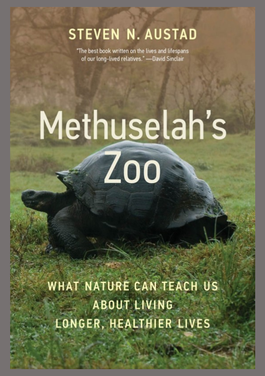
(Seluanov et al., 2018, Fig. 5: Developing anticancer treatments based on naturally evolved cancer resistance.)

Reproduced with permission from Springer Nature, from: Seluanov, A. et al. (2018). Mechanisms of cancer resistance in long-lived mammals. *Nat. Rev. Cancer*, *18*, 433–441.



Finch, CE. (1990). University of Chicago Press.



Austad, SN. (2022). MIT Press.

Within vs. between species:

Sometimes the same fine-tuning dials for within-species plasticity or polymorphism may also be involved in the evolution of long-lived species: microbats have evolved in the same insulin-like signaling pathway involved in the CR response (Seluanov et al., 2018). But they may not always: the most consistently high longevity specific selectivity score in mammals was for FAM126B (family with sequence similarity 126 member B), "an unstudied protein" related to hyccin (Li & de Magalhães, 2013).

Comparative genomics:

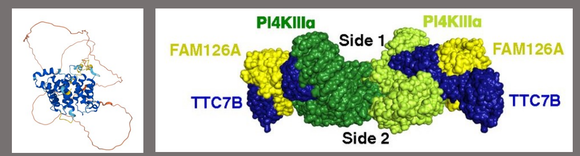
Many non-model organisms' genomes are sequenced: e.g. naked mole rats, Brandt's bats, bowhead whales, eighty-eight species of rockfish. Genomic comparisons can inspire hypotheses; gene editing could test them, along with studying long-lived species' cells in culture.

Some knowns and unknowns:

Naked mole-rats' high molecular mass hyaluronan gives their cells "early contact inhibition" against proliferation; elephants resist cancer partly by having 19 extra pseudogene copies of *TP53*, "the guardian of the genome," but we don't know how whales do it (Seluanov et al., 2018). Ocean quahogs resist protein misfolding, but we don't know how (Austad, 2022).

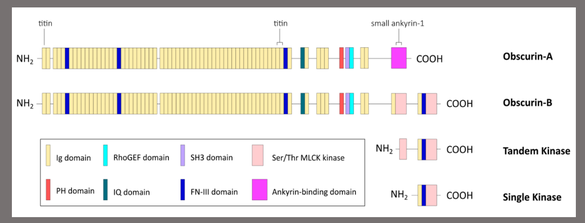
Two genes of interest (Bahry, 2022*b* preprint)**:**

***FAM126B*:** very little-studied; related to *FAM126A* (hyccin, involved in myelination, part of the PI4KIIIα complex). High longevity-specific selectivity score in mammals (Li & de Magalhães, 2013).



Left: FAM126B structure predicted by AlphaFold [UniProt Q8IXS8]. Right: the homolog FAM126A (hyccin) is involved in neural myelination and is part of the PI4KIIIα lipid kinase complex involved in determining plasma membrane identity; reproduced from: Lees, JA. et al. (2017). Architecture of the human PI4KIIIα lipid kinase complex. *Proc. Natl. Acad. Sci. U. S. A.*, *114*, 13720–13725.

***OBSCN*:** obscurin, a giant sarcomeric striated muscle protein, with various other isoforms in various tissues via alternative splicing. Positively selected in long-lived rockfish species; and with a relative evolutionary rate positively correlated both with absolute lifespan, and with residual lifespan independent of body size and swimming depth (Kolora et al., 2021).



Giant and small obscurin isoforms. In striated muscle, tethers the sarcoplasmic reticulum to the sarcomere.