

1920 - “The Rate of Living” Hypothesis

Metabolic activity inversely determines lifespan - not known what the metabolic product was affecting lifespan.

1956 - “Free Radical Theory of Aging”

Denham Harman proposed that ROS produced as byproducts of mitochondrial respiration led to cellular damage which led to deterioration of cellular function and protective responses -> aging phenotypes.

Basis for recent theories such as Caloric Restriction (CR) - alters metabolic pathways in ways that reduce ROS. In yeast, CR leads to longer life AND higher metabolic rates.....

Support for the Free Radical Theory in the last 50 or so years....

Model system: Worms (C. elegans)

- Dauer worms and long lived mutants (Daf-16 mutants) - shifts away from TCA substrates and electron transport, upregulation of antioxidant defenses.
- Increased Insulin Growth Factor (IGF) signaling -> greater dependence on TCA -> shorter lifespan.
- Isp-1 mutants - defective in Complex III, longer-lived, lower oxygen consumption but also slower developmentally.
- Clk-1 mutants - defective in ubiquinone (Coenzyme Q) synthesis, long-lived, but alterations in oxygen consumption or mechanistic electron transport defect still under debate.

Model system: Flies (D. melanogaster)

- Similar gene profile alterations between aged flies and young flies subjected to hyperoxia.
- Overexpression of catalase and SOD enzymes slow aging (however these expts. were done on short-lived strains; less significant effect on normal strains)
- Indy, chico - altered TCA metabolic substrate uptake linked to extended lifespan however in Indy and chico, there is no measurable difference in actual metabolic rates relative to normal strains).
- Methuselah strain - 35% longer-lived, resistant to oxidative and environmental stress, associated with altered changes in G-protein receptor signaling (ligand thought to be a component of the ATP-synthase).
- Increased JNK pathway signaling -> longer lifespan, less oxidative damage

Model system: Mice

- Ames, Snell and Laron dwarf mice - longer-lived, smaller size, lower body temperature, enhanced antioxidant defences (exact enhancement under debate), defects in IGF-signaling.
- Heterozygotic loss of IGF-receptor - long lived mice, increased resistance to oxidative stress.
- SOD2^{+/-} mice - increased oxidative damage, greater tumor incidence, reduced lifespan.
- p66shc-deficient mice - live 30% longer and are resistant to oxidative stress; p66shc involved in IGF- receptor interactions and thought to negatively regulated Forkhead transcription factors which can upregulate SOD and catalase. One piece of evidence suggests that p66shc can be found in the mitochondria directly and affect ROS production.
- Pol gamma defective mice - shortened lifespan plus physical symptoms of aging such as deformed bones, wasted muscles, hair loss and reduced fertility BUT no observed changes in ROS!
- Outbred long-lived mouse strains - higher oxygen consumption but reduced mitochondrial membrane potential to reduce dependence on ATP synthesis coupling - “uncoupling to survive”.

Model system: Human beings

Mostly correlative data....

- Communities with higher antioxidants in diet (Japan, Mediterranean) have higher numbers of centenarians
- Syndromes that affect redox balance or antioxidant defense or damage protection lead to shortened lifespan and premature aging - progeria, Werner's syndrome, Friedrich's ataxia. However, the overt degenerative nature of such diseases make it difficult to ascribe cause and effect.
- Aging associated with many pathologies - neurodegeneration, cardiovascular diseases, metabolic diseases - associated with chronic oxidative stress and damage.
- Limited success with antioxidant pharmacological intervention - too little known about the targets of oxidative stress.

The challenges of distinguishing the many effects of elevated ROS in different pathologies

A need for systems with clearly defined parameters to be tested.
A general rule of thumb: Systems that extend lifespan tend to be more informative than systems that decrease lifespan....