NORN GROUP

Nutrient Sensing

Presented by Madison Ueland on 2/06/2022

Discussion Summary

Paper(s): Finkel, T. The metabolic regulation of aging. *Nat Med* 21, 1416–1423 (2015). https://doi.org/10.1038/nm.3998

Roadmap

- Overview of core nutrient sensing pathways
  - Insulin/IGF-1
  - mTOR
  - Sirtuins and NAD+
  - AMPK
- Big picture takeaways
- Discussion questions

IIS (Insulin/Insulin-Like Growth Factor Signalling)

- Glucose sensing pathway promoting nutrient uptake and anabolic processes
- Attenuation of IIS improves lifespan in model organisms
  - Attenuating IIS signaling through FOX homologs lengthens lifespans of worms and flies
    - E.g. First long-lived *C. elegans*: Tom Johnson's *age-1* (homologous to mammalian PI3K) mutants; Cynthia Kenyon's *daf-2* (homologous to IGF-1 receptor) mutants, mediated by downstreated TF Daf-16 (homologous to FOXO)
  - PI3K mice have weakened IIS pathway and live longer
  - Long-lived Ames dwarf mouse has reduced IIS (among other defects)
    - Restoring GH levels* in Ames mice reverted longevity to that of non-mutant controls
  - Targeted approaches altering IGF receptor or IGF-1 bioavailability increase longevity with **strain and sex specific effects**
- Smaller individuals within species live longer
  - Small dogs, ponies
  - Mutant mice: Ames dwarf, Snell dwarf, mice lacking GH receptor

*GH ≠ IIS: see this review for details

IIS (2)

- High IGF-1 activities can be harmful
  - Increases diabetes, cancer by promoting pathways leading to cell production
- It's complicated
  - E.g. Full-body knockout of insulin receptor (Insr) is lethal in mice, many tissue-specific knockouts have poor health, but the fat-specific *Insr* knockout (FIRKO) mouse is long-lived and resistant to obesity
  - Full-body knockouts of IIS genes often bad… **tissue-specific modulation more promising** e.g. brain specific KO Irs2 mice live longer (14% for homozygotes, 18% for heterozygotes)
- IGF-1 in humans
  - Reduced IGF-1 activity in people without functional GH receptors (Laron syndrome) who have low incidence of age-related disease (cancer, T2D)
  - BUT other genetic disorders caused by mutations in the insulin receptor lead to insulin resistance and short lifespan e.g. Donohue syndrome ('Leprechaunism'), Rabson-Mendenhall syndrome
  - GWAS studies correlate mutations in IGF-1 receptors of FOXO TFs with healthspan and longevity
  - Human female nonagenarians with below-median IGF-1 levels had significantly longer survival than those with above-median levels (but effect was not found in males)
- Circulating IGF-1 levels peak at the second decade of life, then rapidly decline and plateau

mTOR

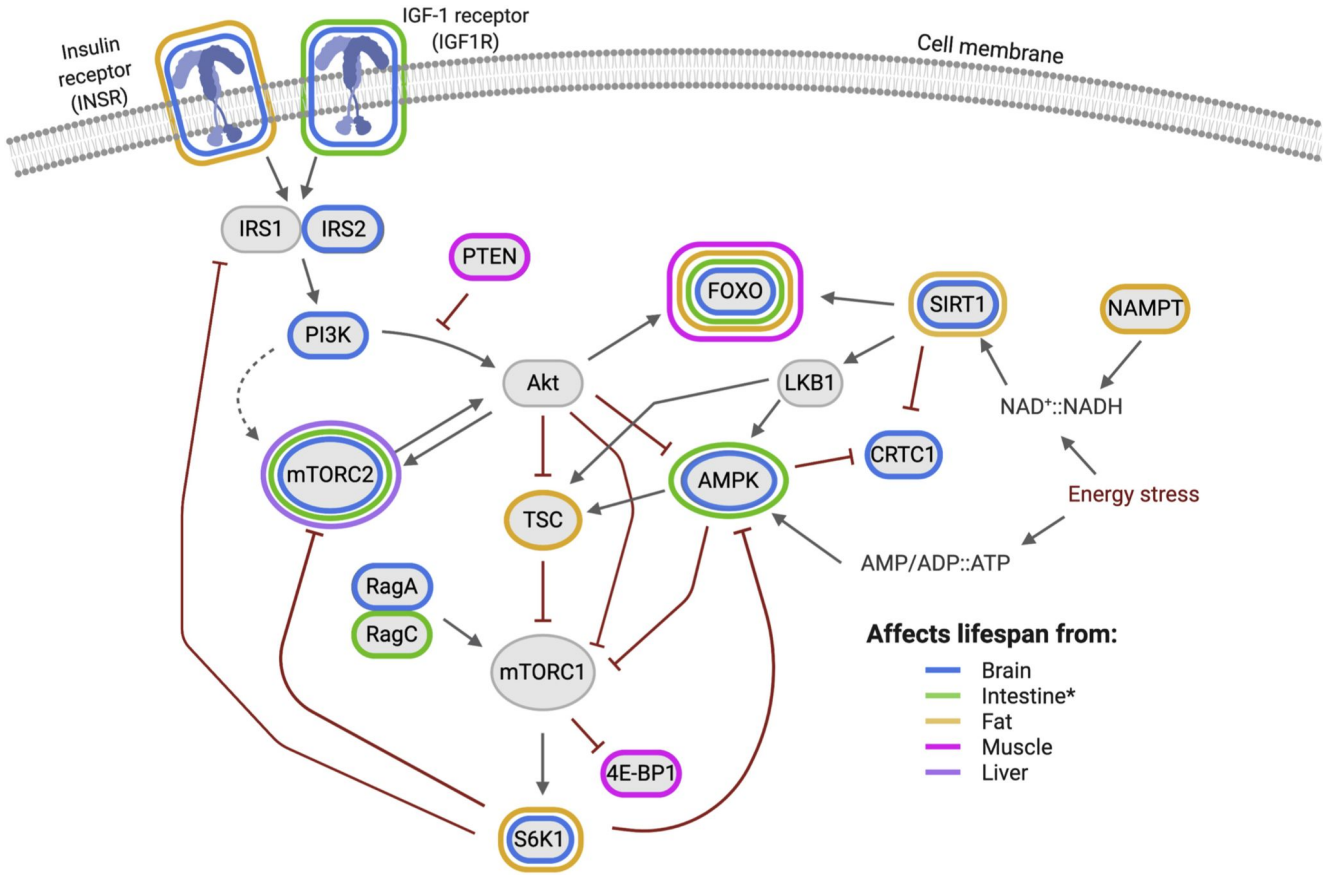
- Serine-threonine kinase activated by rise in intracellular amino acid levels or growth factor stimulation
  - Regulates anabolic metabolism, like IIS
- In mammals, composed of two protein complexes: mTORC1, mTORC2
  - mTORC1 most studied in aging
- Inhibiting mTOR extends lifespan in model organisms
  - Mice, yeast, worms, flies
  - Adding dietary restriction to genetic inhibition of mTOR in yeast and worms does not further increase lifespan: mediator of CR benefits? *Has this been tried in mice?*
- Caveats: inhibiting mTOR not always beneficial*
  - Rapamycin (at immunosuppressant dose, which is larger than suggested anti-aging dose) disrupts glucose homeostasis, causes hyperlipidemia in humans and mice
  - Impairs healing, causes cataracts and testicular generation in mouse models

*not mentioned in Finkel review

mTOR (2)

- Mechanism by which reduced mTOR signaling extends lifespan not very clear?
  - Regulates a number of downstream targets that are linked to regulating protein synthesis, mitochondria function, substrate utilization, insulin signaling, autophagic flux
- Role of mTOR in metabolism is tissue and species specific
  - Mammalian cell lines: mTOR positively regulates mitochondrial respiration
  - Yeast: mTOR negatively regulates oxygen consumption
  - Mice: disruption of mTORC1 activity in mice has contrasting effects on mitochondrial function in skeletal muscle and adipose tissue
- Can act in non-cell-autonomous function
  - E.g. CR mediates mTORC1 activity in cells surrounding intestinal stem cells, boosting iSC function
  - Invertebrate studies have found profound metabolic effects from targeting mTORC1 signaling in a single tissue
- Crosstalk with other pathways
  - E.g. extending lifespan of *C. elegans* by inhibiting mTOR requires AMPK

Metabolic pathways and tissues implicated in aging



Sirtuins and NAD+

- NAD+ is cofactor central to many metabolic pathways, NAD+/NADH ratio signals cell to shift between glycolytic and oxidative metabolism
- Sirtuins = NAD+ dependent deacetylases of histones and non-histone proteins
- NAD+ levels and sirtuin activity increase with CR
- Upregulating sirtuins good, but only weak effects?
  - SIRT1
    - First implicated in longevity through Sir2 in yeast
    - Upregulating SIR2 (homolog of mammalian SIRT1) in worms only leads to slight gains in longevity
    - Mice lacking SIRT1 expression do not experience increase in lifespan from CR!
    - Overexpressing SIRT1 in mice improves health span but not lifespan
  - SIRT6 promotes longevity
    - Deficient mice age faster
    - Overexpression extends lifespan in male mice
  - Sirtuins (3,4,5) localized in mitochondria have widespread metabolic effects
    - SIRT3 improves regeneration of old hematopoietic cells?
    - SIRT3 activation required to achieve beneficial effects of CR on hearing loss, transcriptional program induced by CR requires SIRT 3?
- Decline in NAD+ levels is associated with aging
  - But supplementation with NAM (NAD+ precursor) did not extend lifespan of male mice (just healthspan)

AMPK (AMP activated protein kinase)

- Sensor of CR restricted states and catabolism
  - Binds AMP (adenosine monophosphate) and ADP (adenosine diphosphate), which are lower-energy adenine nucleotides increase in proportion to higher energy forms (ATP) when intracellular energy stores are depleted
- When activated, AMPK regulates metabolic pathways that increase energy supplies and reduce energy demand
- Higher activity of AMPK correlated with longevity
  - Metformin activates AMPK in mice and worms
  - CR increases AMPK activity but depends on tissue and CR protocol
  - In worms and flies, some kinds of dietary restriction require activation of AMPK orthologs to achieve lifespan extension, but **depends on degree of DR and composition of diet**

Autophagy: Key downstream process of AMPK

- Upregulating AMPK in multiple tissues induces autophagy both cell autonomously and non-autonomously
  - e.g. bidirectional relationship between AMPK activation and autophagy in intestine and neurons
- Autophagy also important to other pathways
  - E.g. IIS: mutations in Daf-2 in worms depends on functioning autophagic system, beneficial effects of CR in worms or yeast do not occur when autophagy is inhibited
  - E.g. mTOR and AMPK regulate (inhibit and activate, respectively) ULK1 (unc-51 like autophagy activating kinase 1), an upstream component of autophagy conserved across species

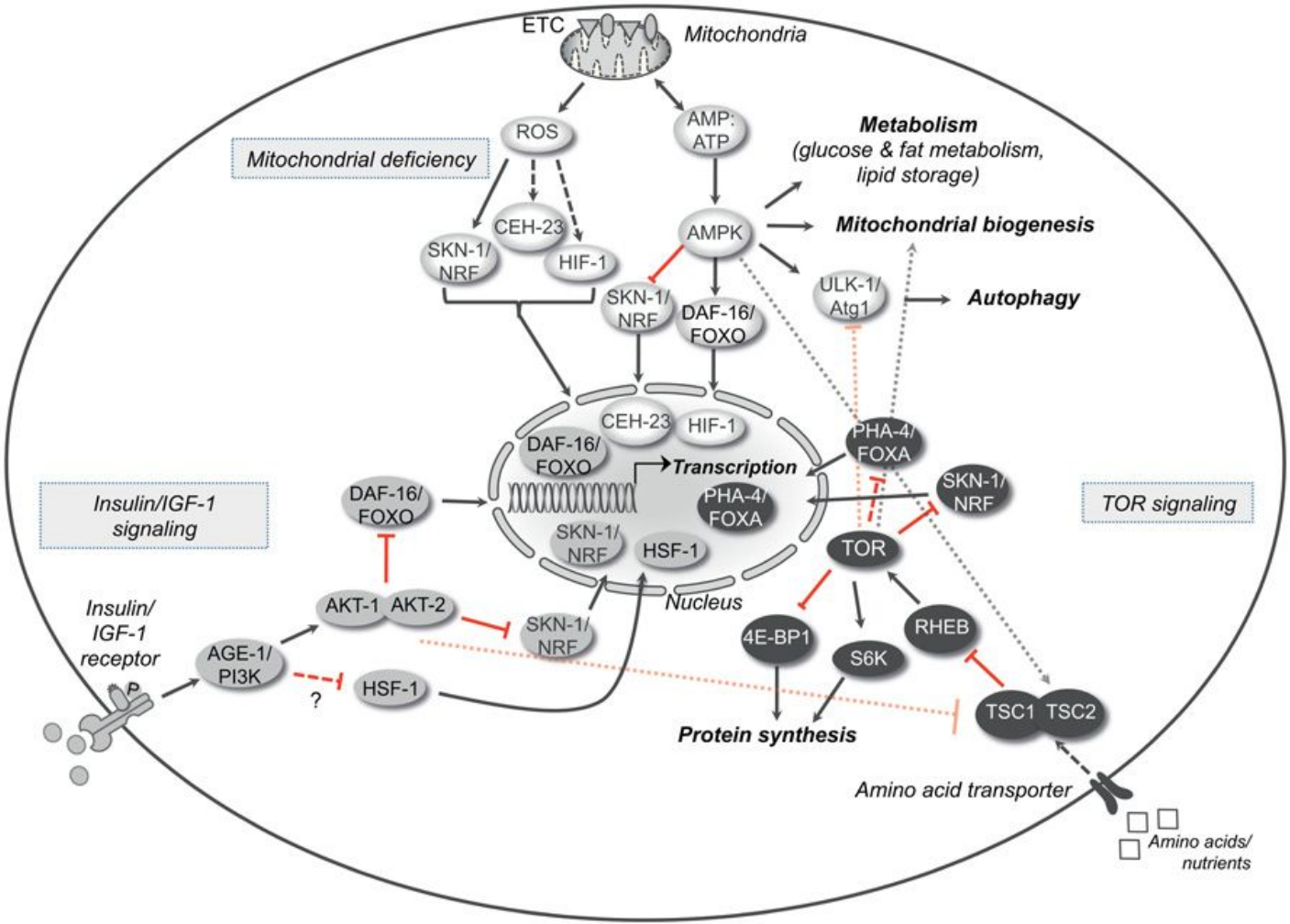
Big Picture Takeaways

- Tradeoffs… interventions often pleiotropic
- Context dependence
  - Fine line between deleterious and pro-longevity interventions: often dependent on sex, food source, tissue
- Distil, non-cell-autonomous effects
  - Can we uncouple negative health effects from longevity with tissue specific modulation?
- Complex crosstalk between pathways
  - E.g. AMPK = regulator and target of mTOR signaling
- Bear sources in mind…
  - Finkel review optimistic

What frameworks can we use to understand metabolic pathways?

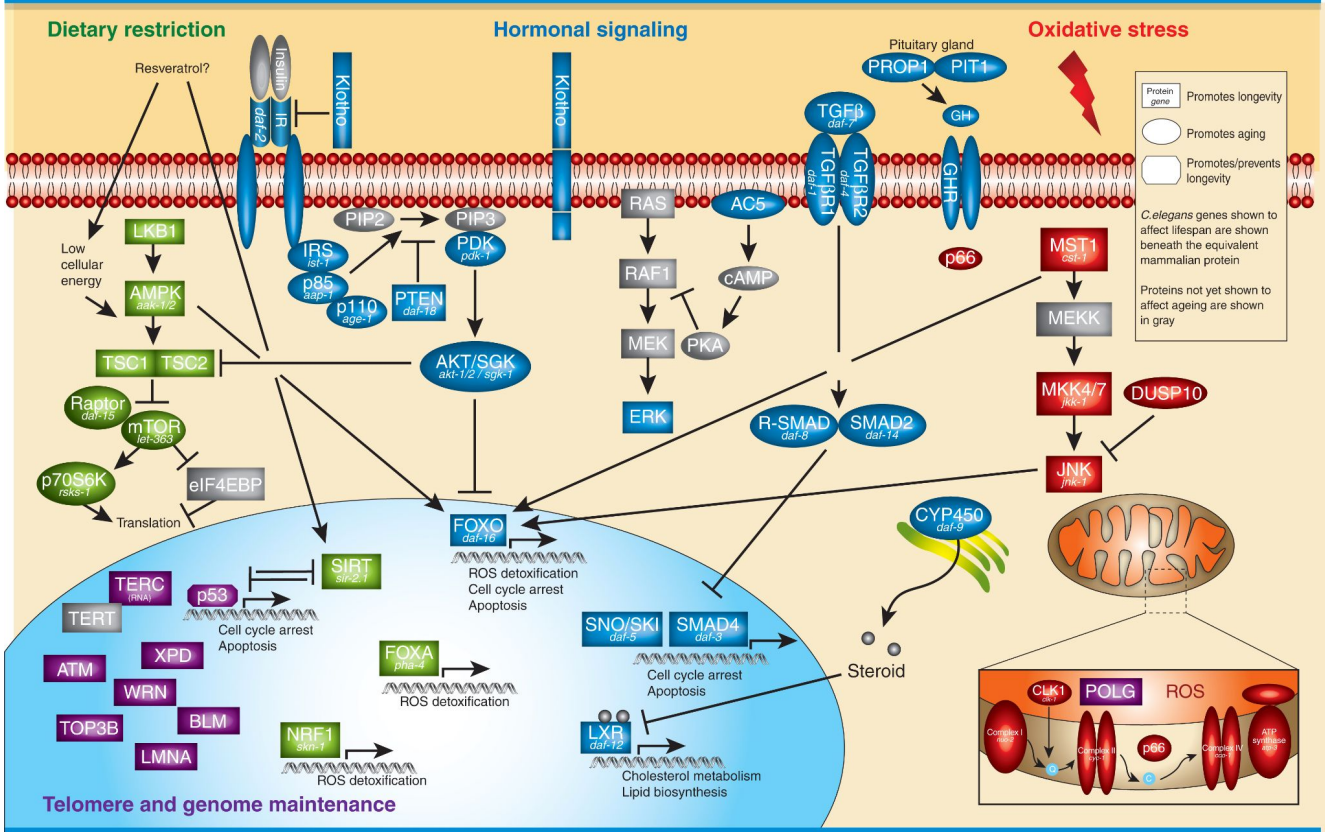
Feels artificial to separate in this way, but need to have starting point…

What degree of life extension can we expect from metabolic interventions?


ETC
Mitochondria
ROS
AMP:
ATP
Mitochondrial deficiency
Metabolism
(glucose & fat metabolism,
lipid storage)
CEH-23
SKN-1/
NRF
HIF-1
AMPK
Mitochondrial biogenesis
ULK-1/
Atg1
Autophagy
SKN-1/
NRF
DAF-16/
FOXO
CEH-23
HIF-1
DAF-16/
FOXO
Transcription
PHA-4/
FOXA
SKN-1/
NRF
TOR signaling
Insulin/IGF-1
signaling
DAF-16/
FOXO
PHA-4/
FOXA
SKN-1/
NRF
HSF-1
TOR
Nucleus
Insulin/
IGF-1
receptor
AKT-1
AKT-2
SKN-1/
NRF
4E-BP1
RHEB
AGE-1/
PI3K
?
HSF-1
S6K
TSC1
TSC2
Protein synthesis
Amino acid transporter
Amino acids/
nutrients

Signaling Networks in Aging

Eric L. Greer and Anne Brunet



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