Effects of Nutritional Interventions on Aging

Brennen McKenzie, MA, MSc, VMD

Sponsored by

Transforming Lives

Effects of Nutritional Interventions on Aging

Brennen McKenzie

FINAL DISCLOSURE:

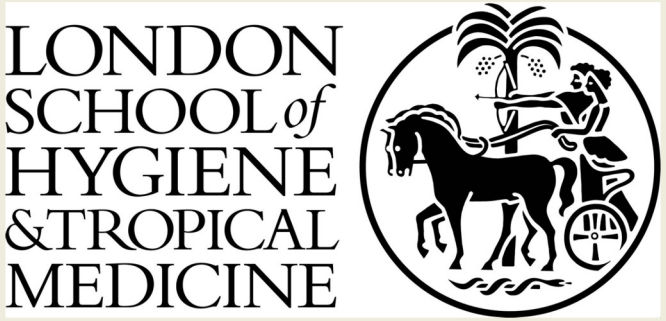
Part-time employment- Loyal

UNLABELED/UNAPPROVED USES DISCLOSURE:

None

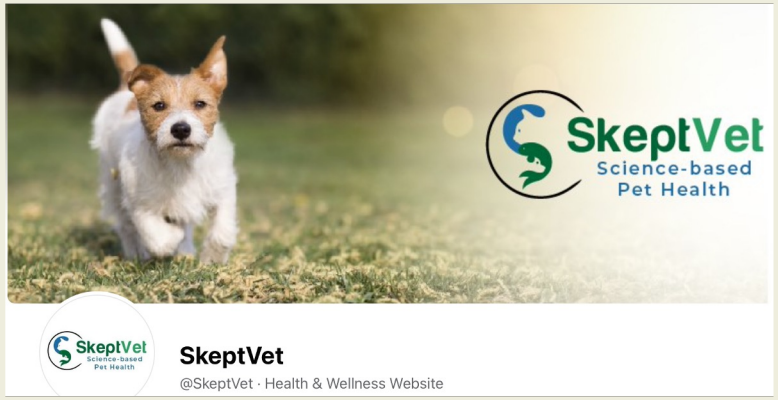
Who is This Guy?

- VMD
- MSc Epidemiology
- MA Physiology & Behavior



Who is This Guy?

- Adobe Animal Hospital
- Loyal
- EBVMA
- SkeptVet



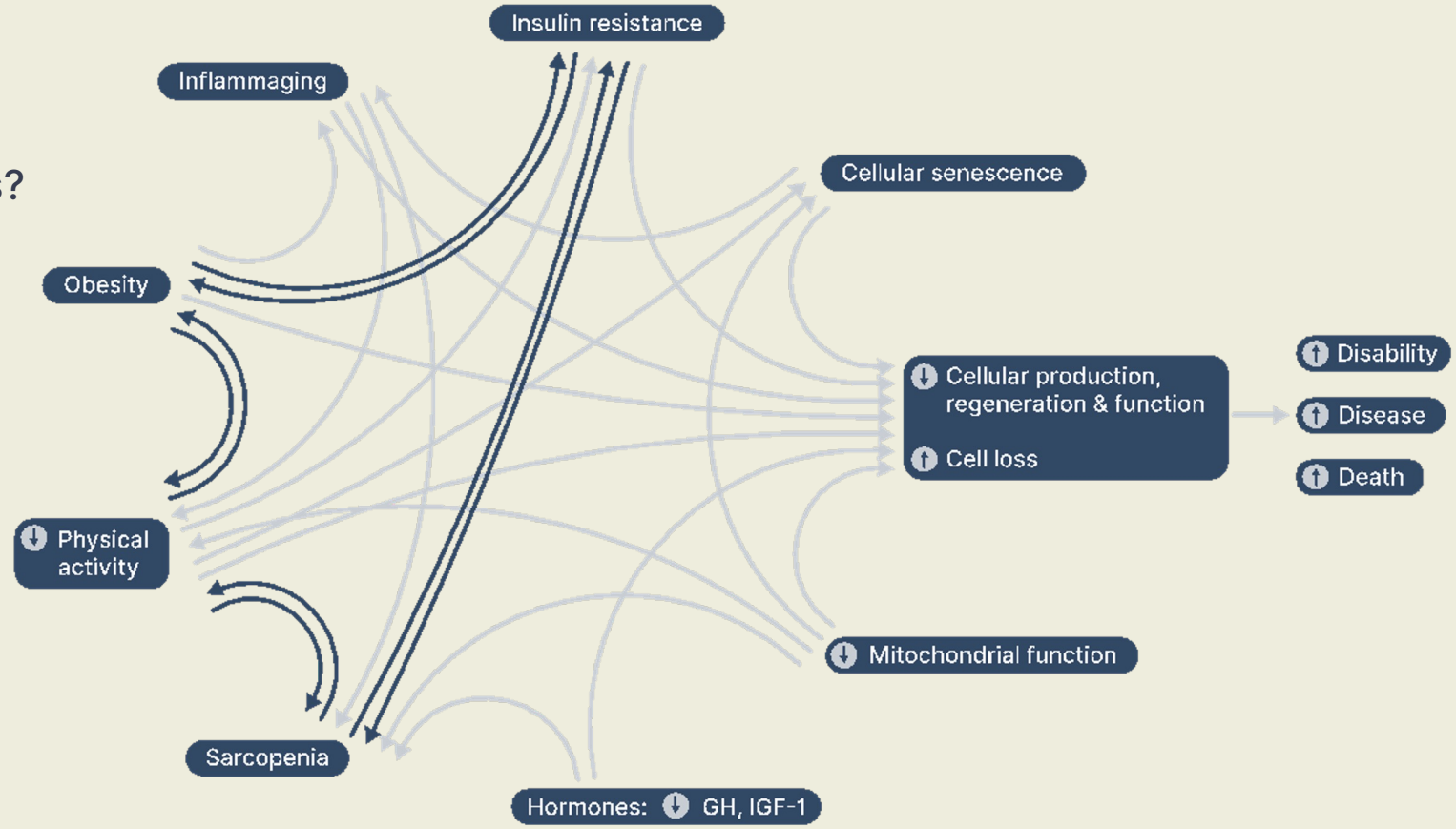
Aging and Nutrition

- What is aging?

Jones A. *Dog Years: Faithful Friends, Then & Now*. Chronicle Books; 2015.

Aging and Nutrition

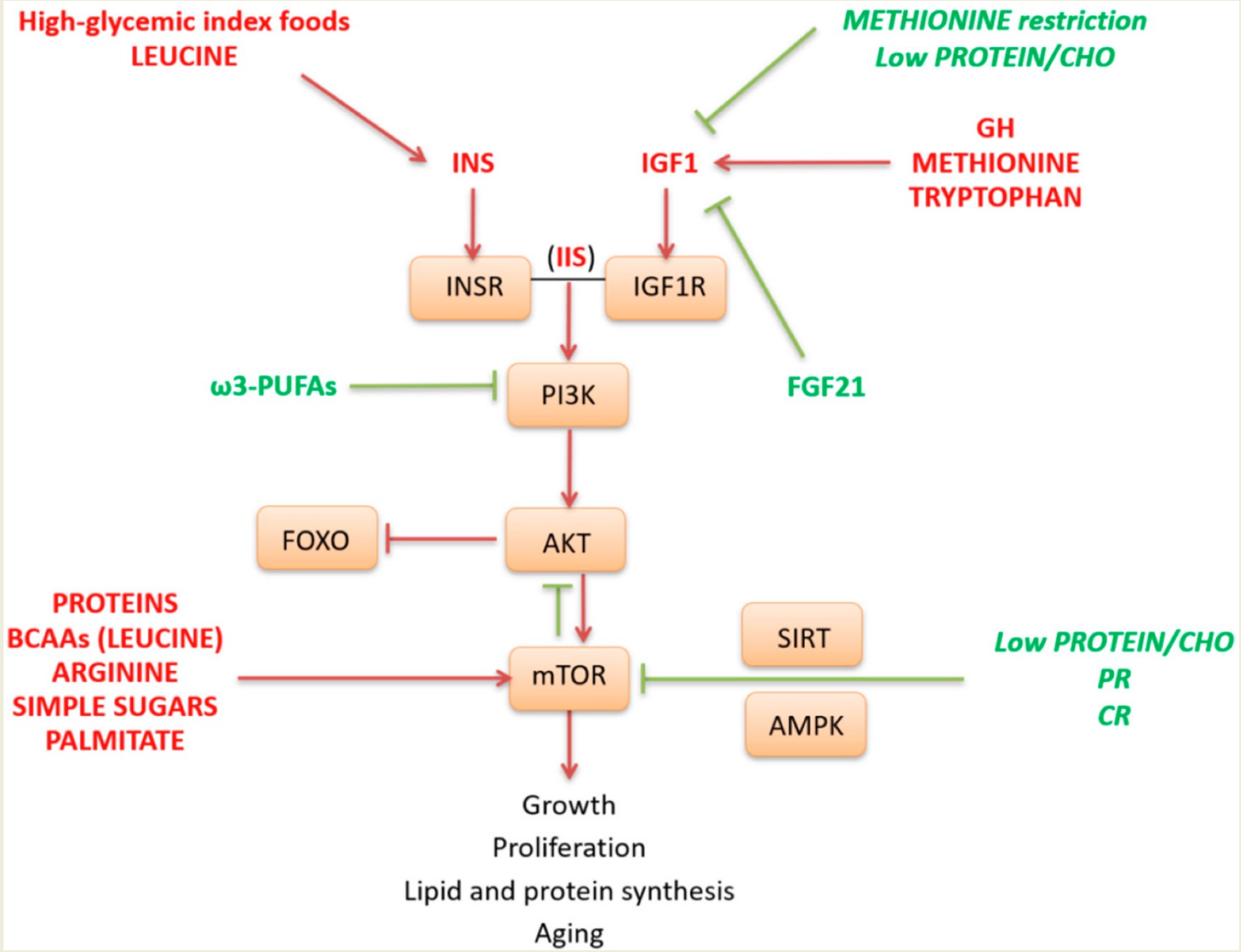
- What is aging?
- What are the underlying mechanisms?



McKenzie BA. Comparative Veterinary Geroscience: Mechanism of molecular, cellular, and tissue aging in humans, laboratory animal models, and companion dogs and cats. Amer J Vet Res. 2022;83(6:).

Aging and Nutrition

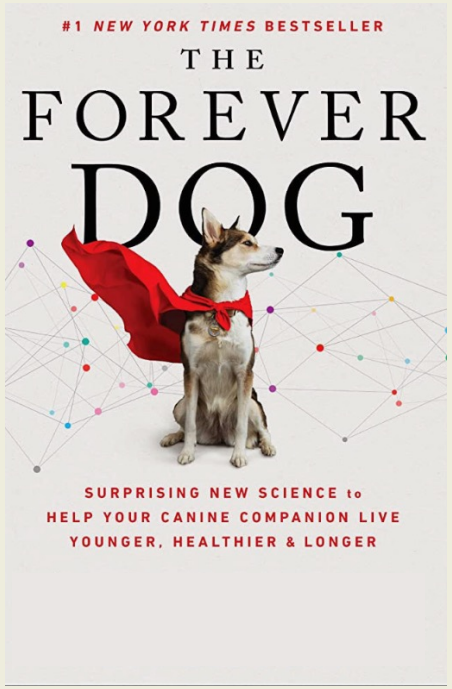
- What is aging?
- What are the underlying mechanisms?
- How does nutrition influence these?

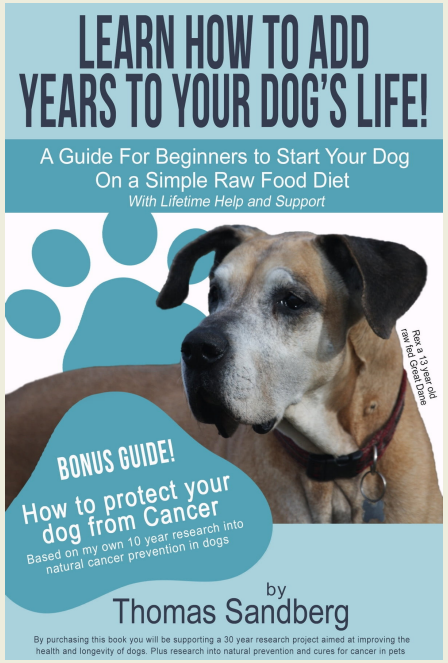


Pignatti C, D'Adamo S, Stefanelli C, Flamigni F, Cetrullo S. Nutrients and Pathways that Regulate Health Span and Life Span. Geriatrics (Basel). 2020;5(4):95.

Aging and Nutrition

- What is aging?
- What are the underlying mechanisms?
- How does nutrition influence these?
- What are the implications?





WHAT IS AGING?

What Is Aging?

→ Scientific Literature

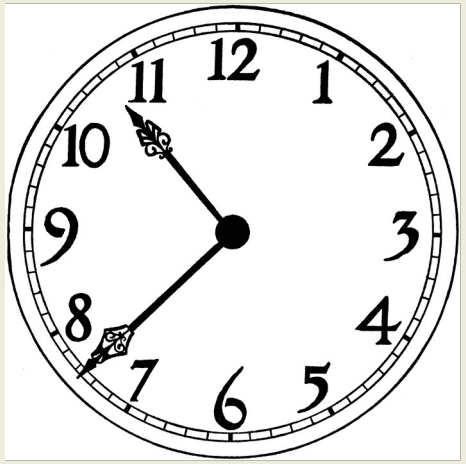
- The progressive **accumulation of changes** with time associated with or responsible for the **ever-increasing susceptibility to disease and death**

- A persistent decline in the age-specific fitness components of an organism due to **internal physiological degeneration**

- A process of the **progressive functional decline with time**, leading to **disability, dependence, morbidity, and mortality**

What Is Aging?

- Time Passing
- Physical & Functional Changes
- Increase Risk of Three Ds
  - Disability
  - Disease
  - Death



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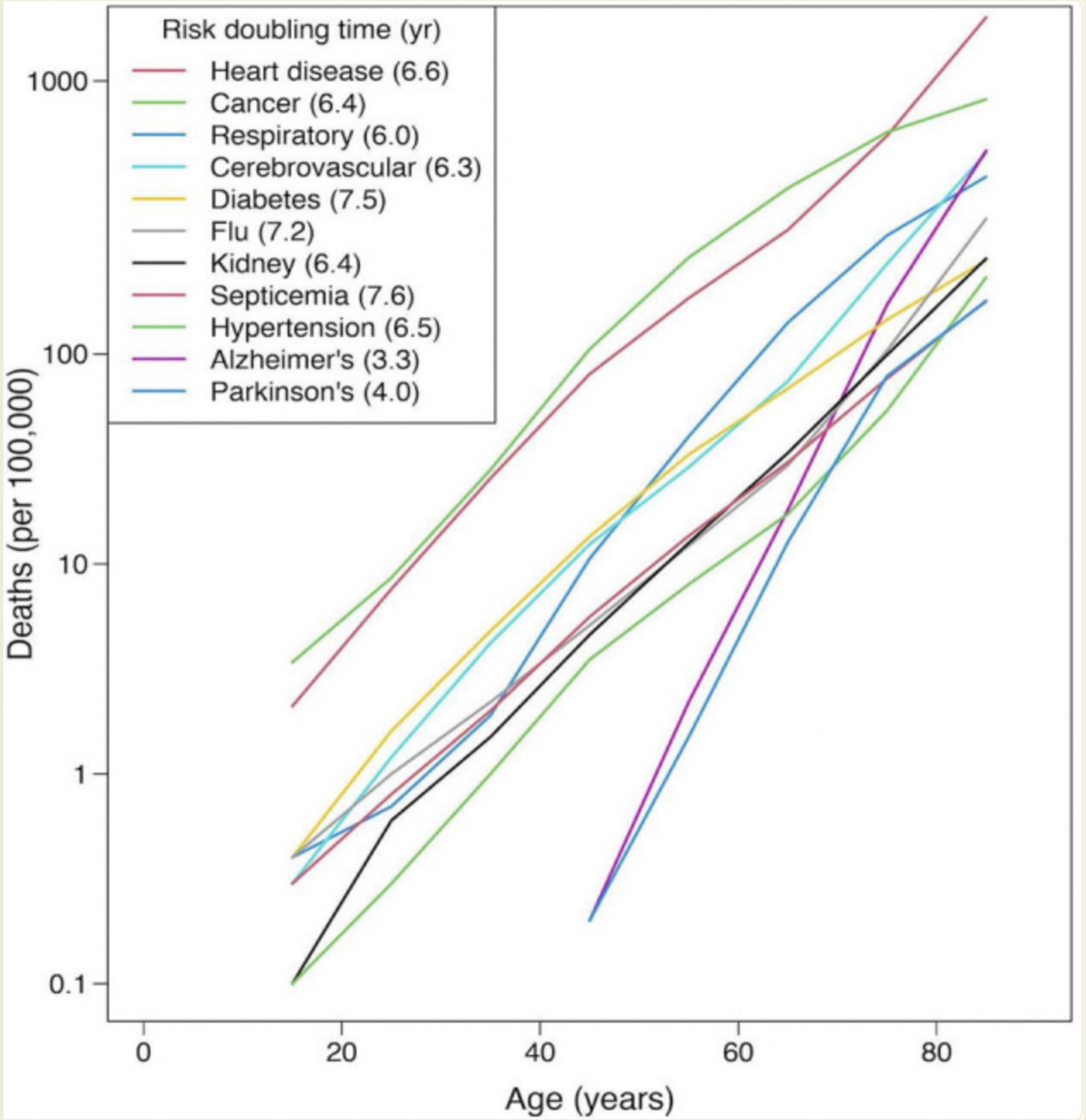

McCune S, Promislow D. Healthy, Active Aging for People and Dogs. *Front Vet Sci*. 2021;8:655191.

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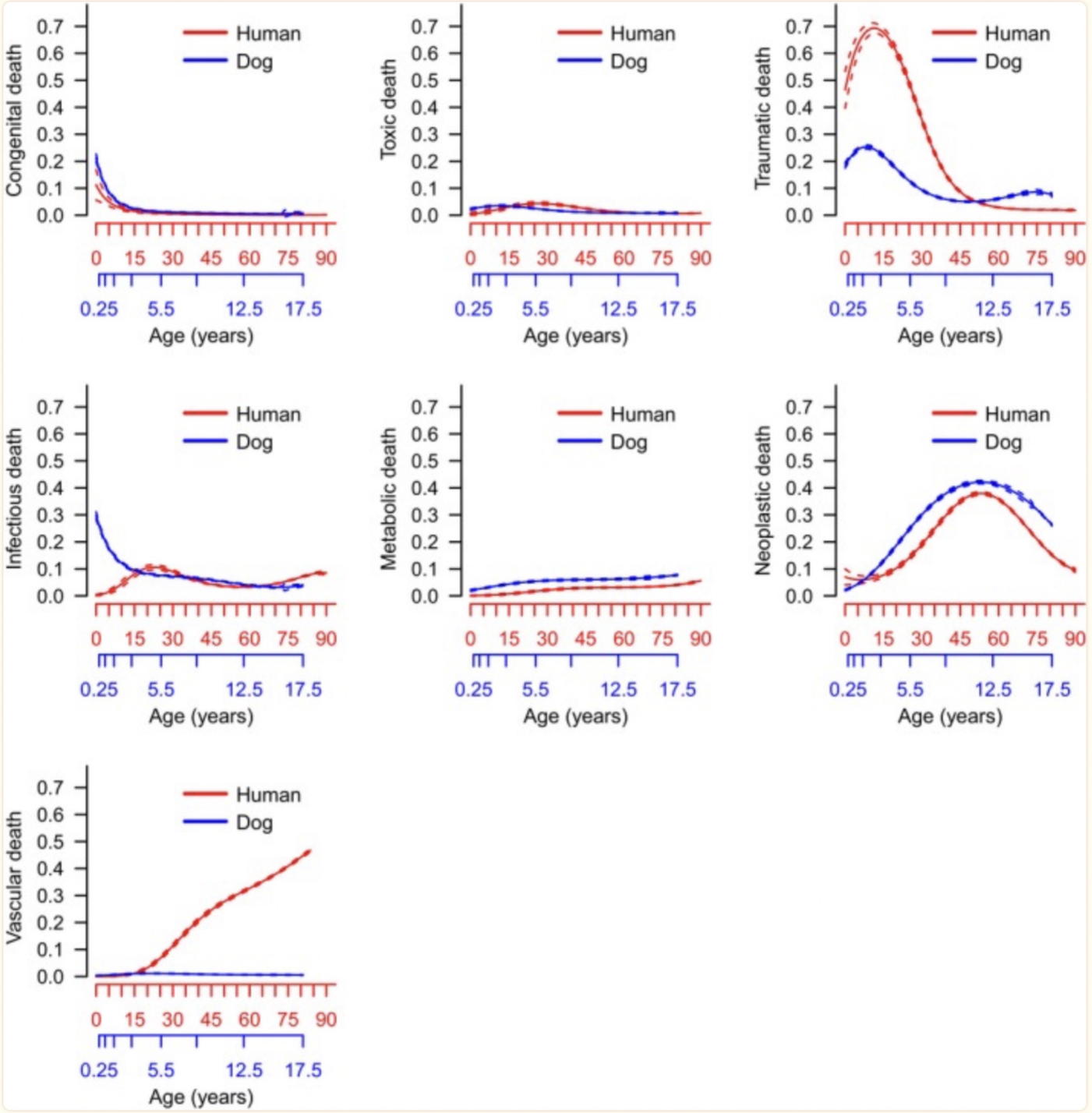
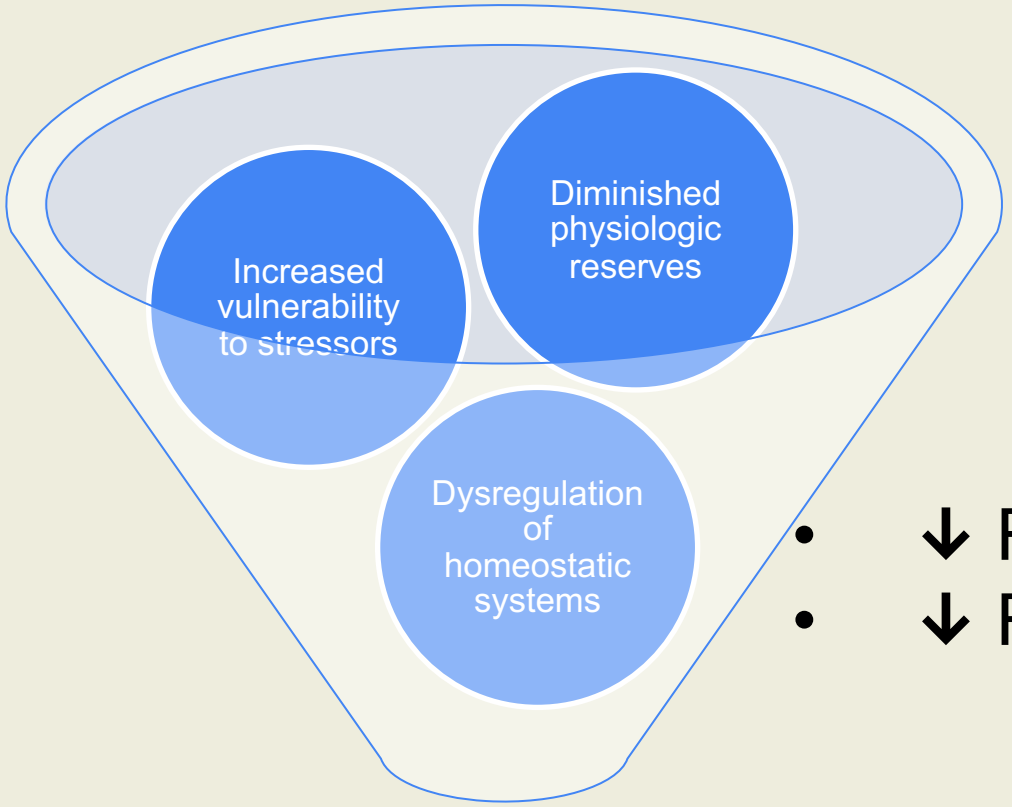


Hoffman JM, Creevy KE, Franks A, O'Neill DG, Promislow DEL. The companion dog as a model for human aging and mortality. Aging Cell. 2018 Jun;17(3):e12737.

What Is Aging?

- Time Passing
- Physical & Functional Changes
- Increase Risk of Three Ds
  - Disability
  - Disease
  - Death
- Frailty

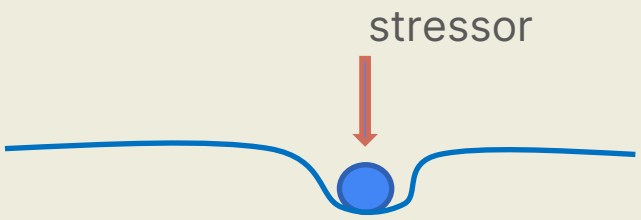


- ↓ Robustness
- ↓ Resilience

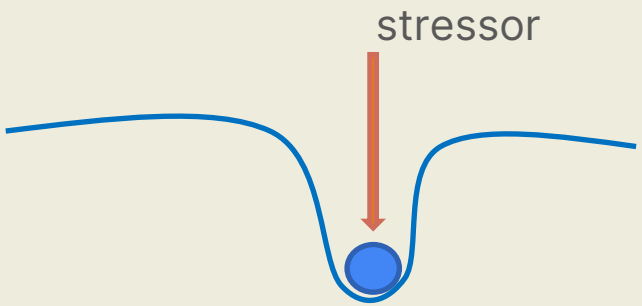
Frailty ⟺

- Disability
- Disease
- Death

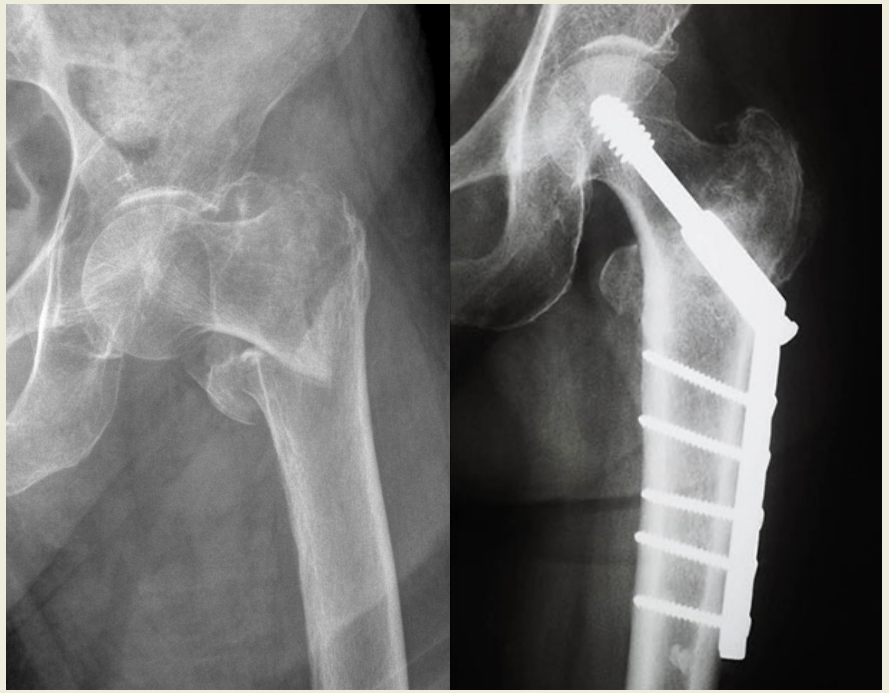
Normal State

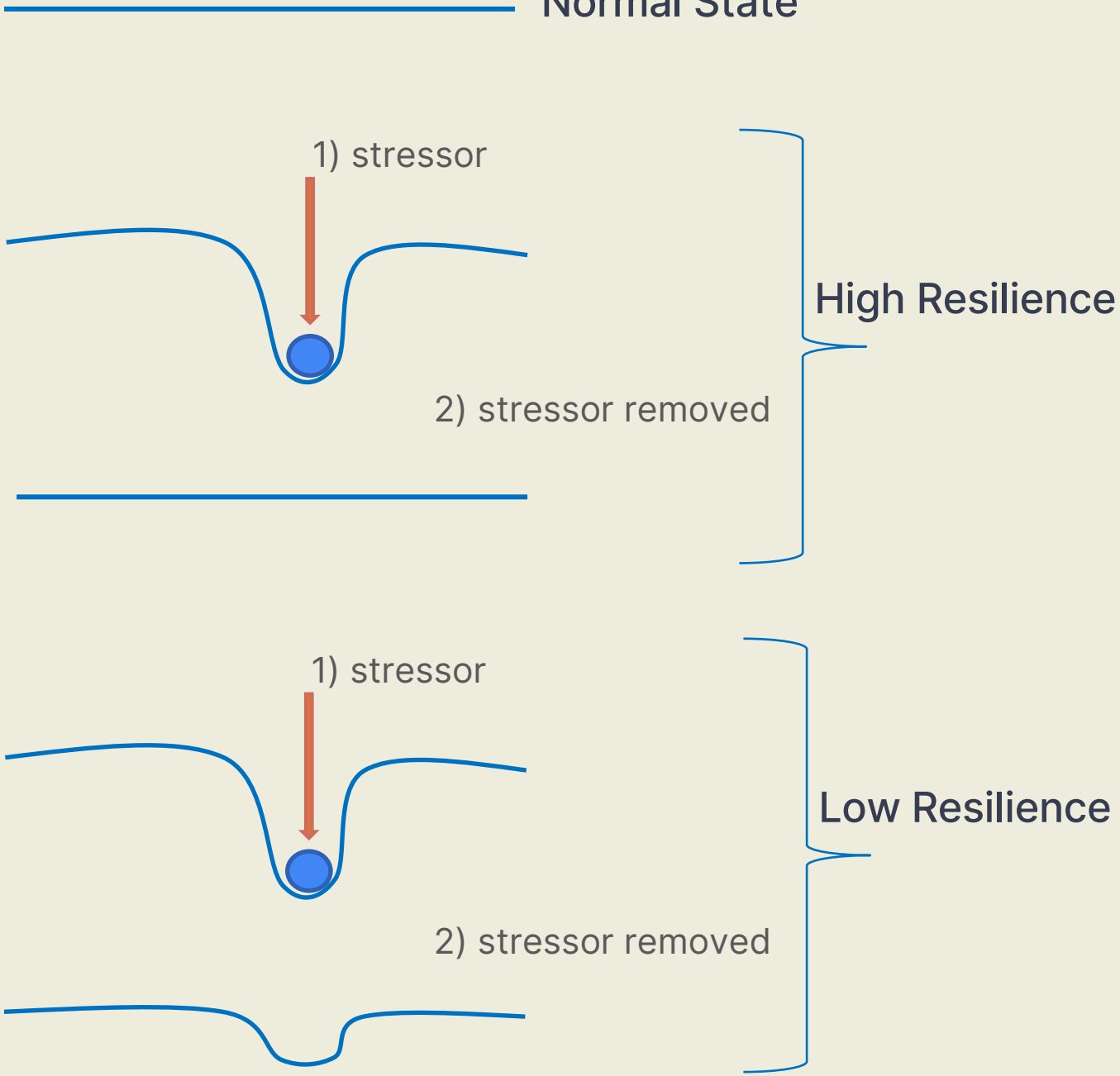


High Robustness

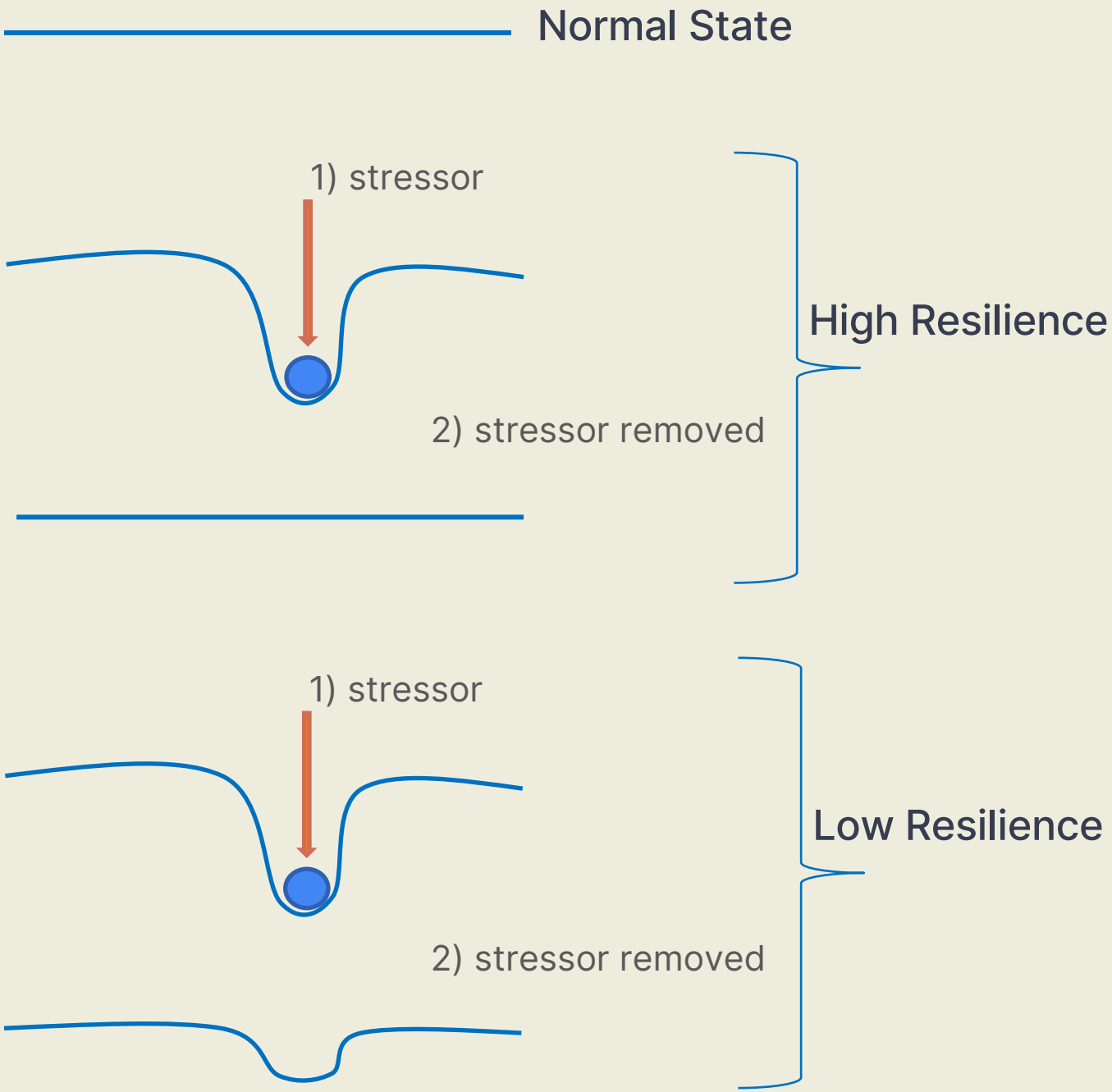


Low Robustness




Normal State
1) stressor
2) stressor removed
High Resilience
1) stressor
2) stressor removed
Low Resilience


Day 1
6 Months


Normal State
1) stressor
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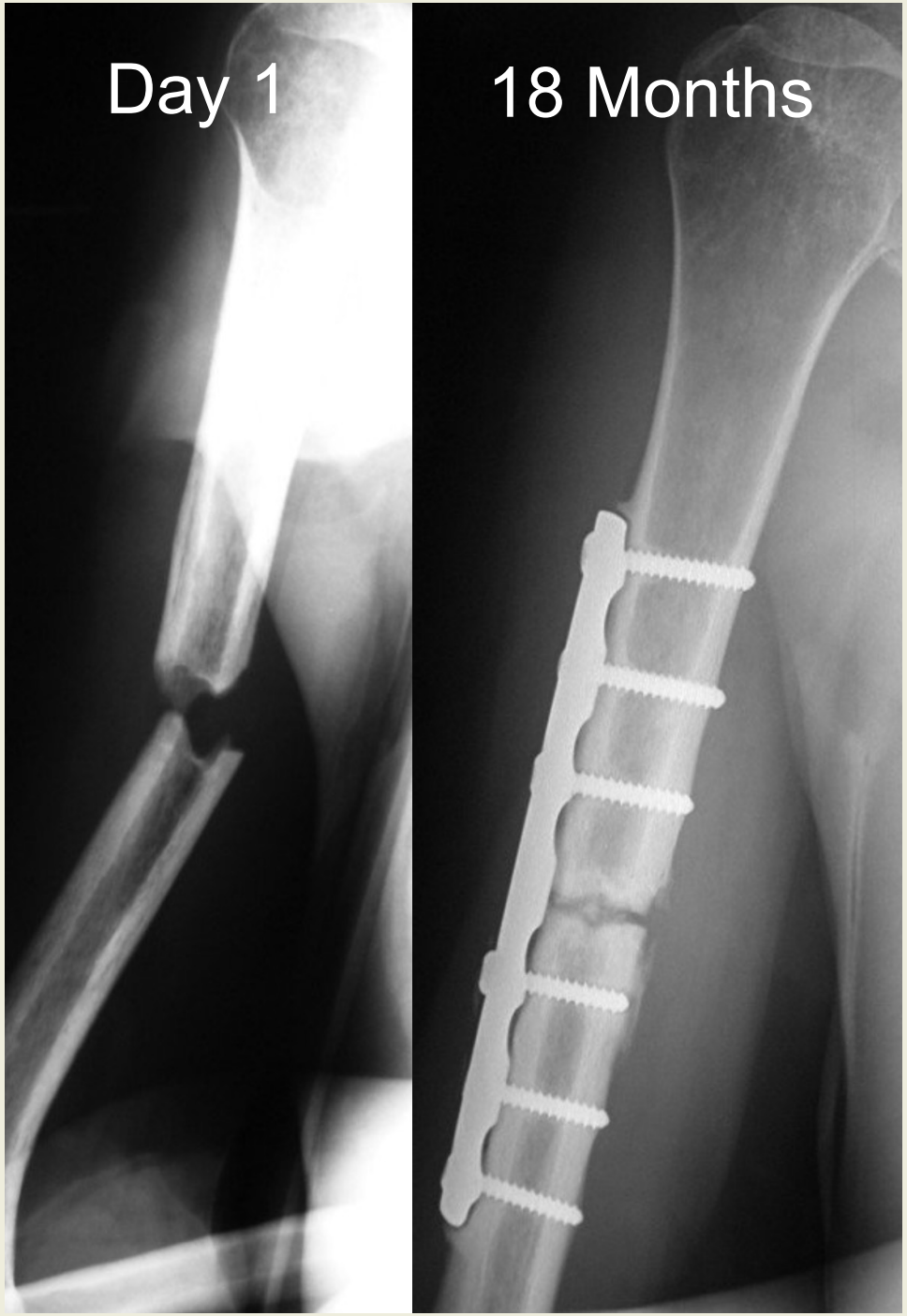

Day 1
18 Months

Nutrition & Aging

How Diet Can Impact Aging

- Treatment and prevention of age-associated disease
- Optimization of diet for life stages
- Optimization of diet for individuals
- Targeting mechanisms of aging

How Diet Can Impact Aging

- ~~Treatment and prevention of age-associated disease~~
- ~~Optimization of diet for life stages~~
- ~~Optimization of diet for individuals~~
- Targeting mechanisms of aging

Mechanisms of Aging

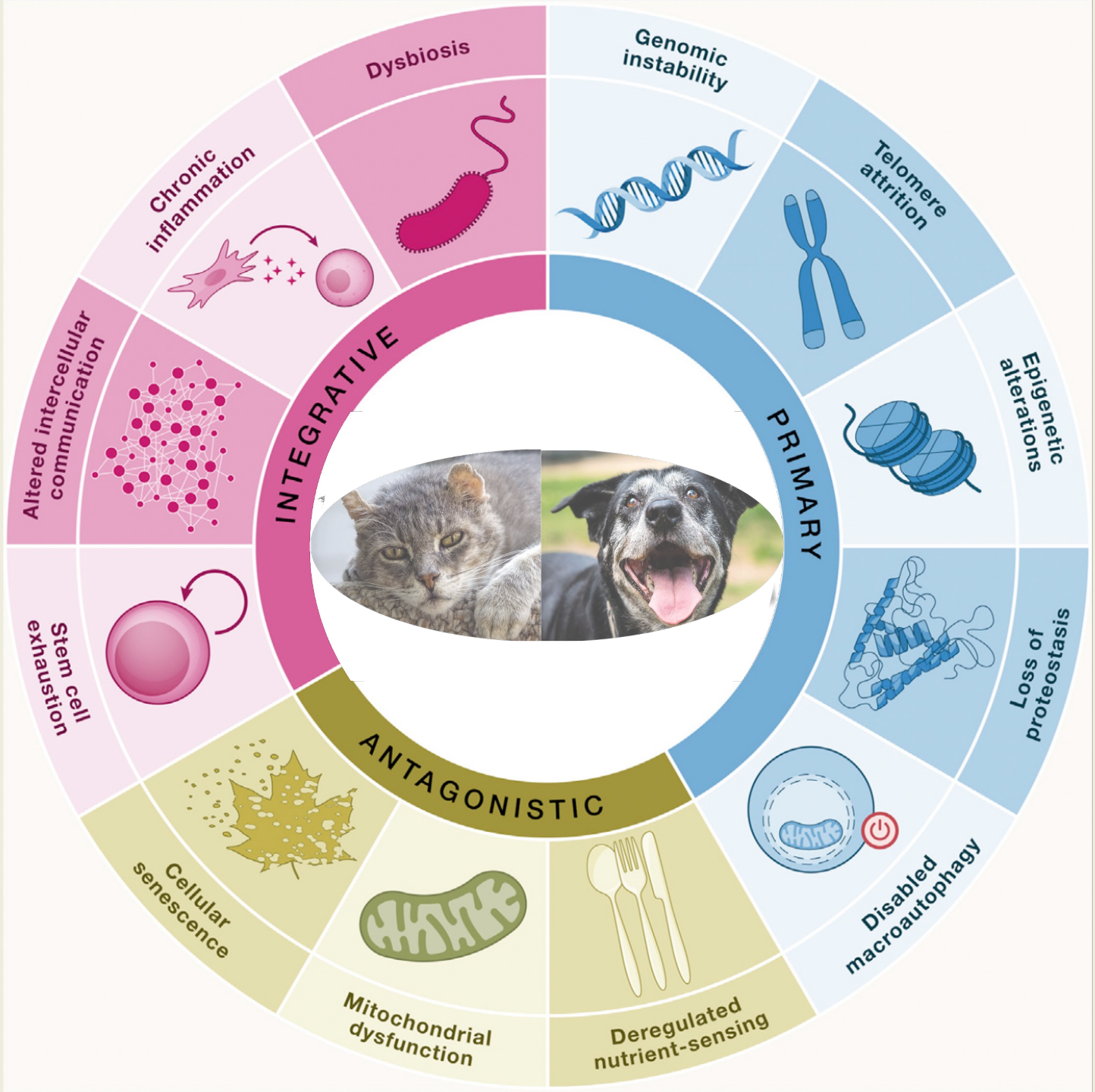
Mechanisms of Aging

- It's Just Biology!

- Cellular & Molecular Mechanisms

- Tissue Aging

- Organismal Aging
  - Phenotype

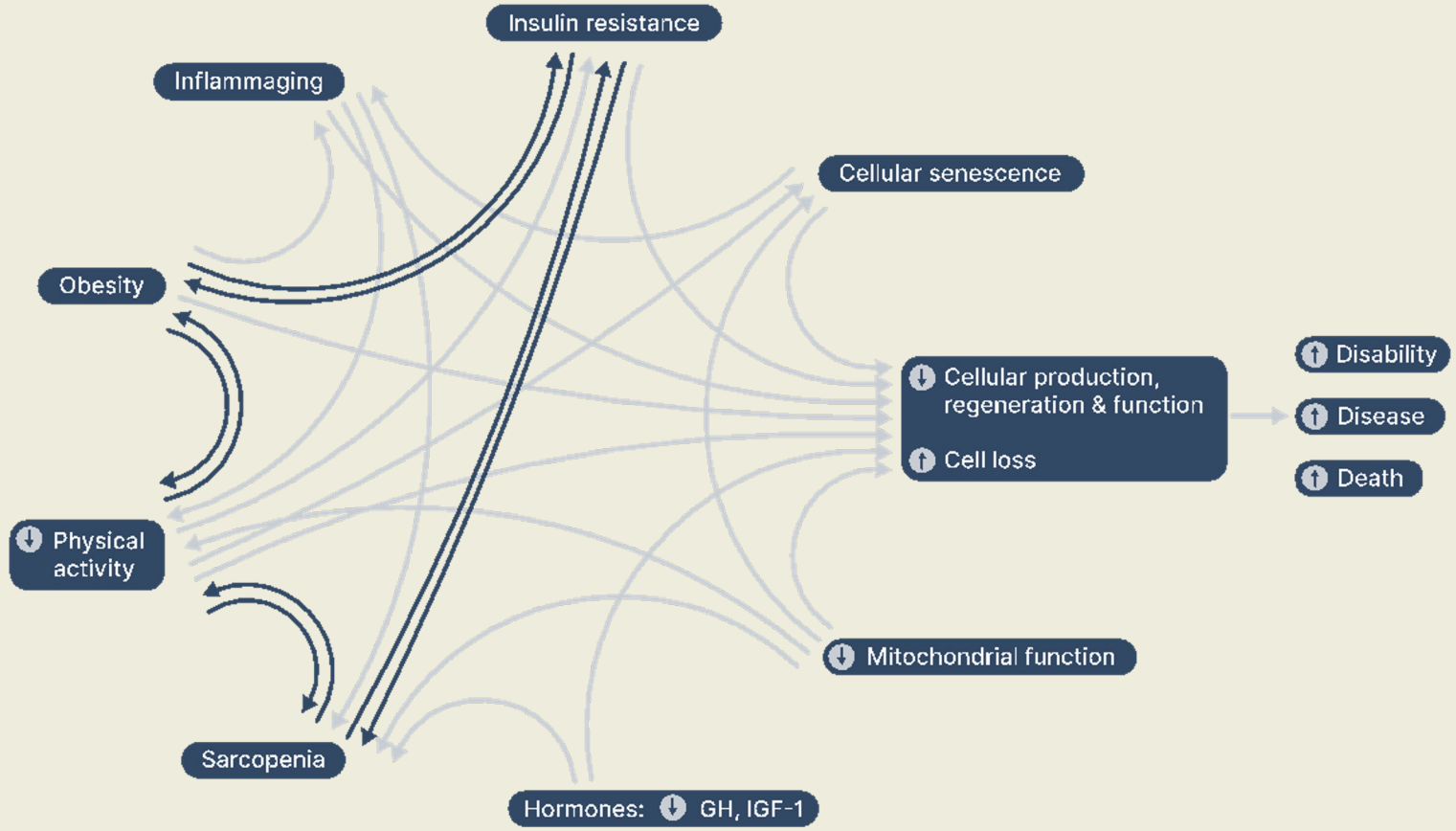


López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186(2):243-278.

Aging Mechanisms

Web of Aging

- Cellular & Molecular Mechanisms
- Environment
- Chance



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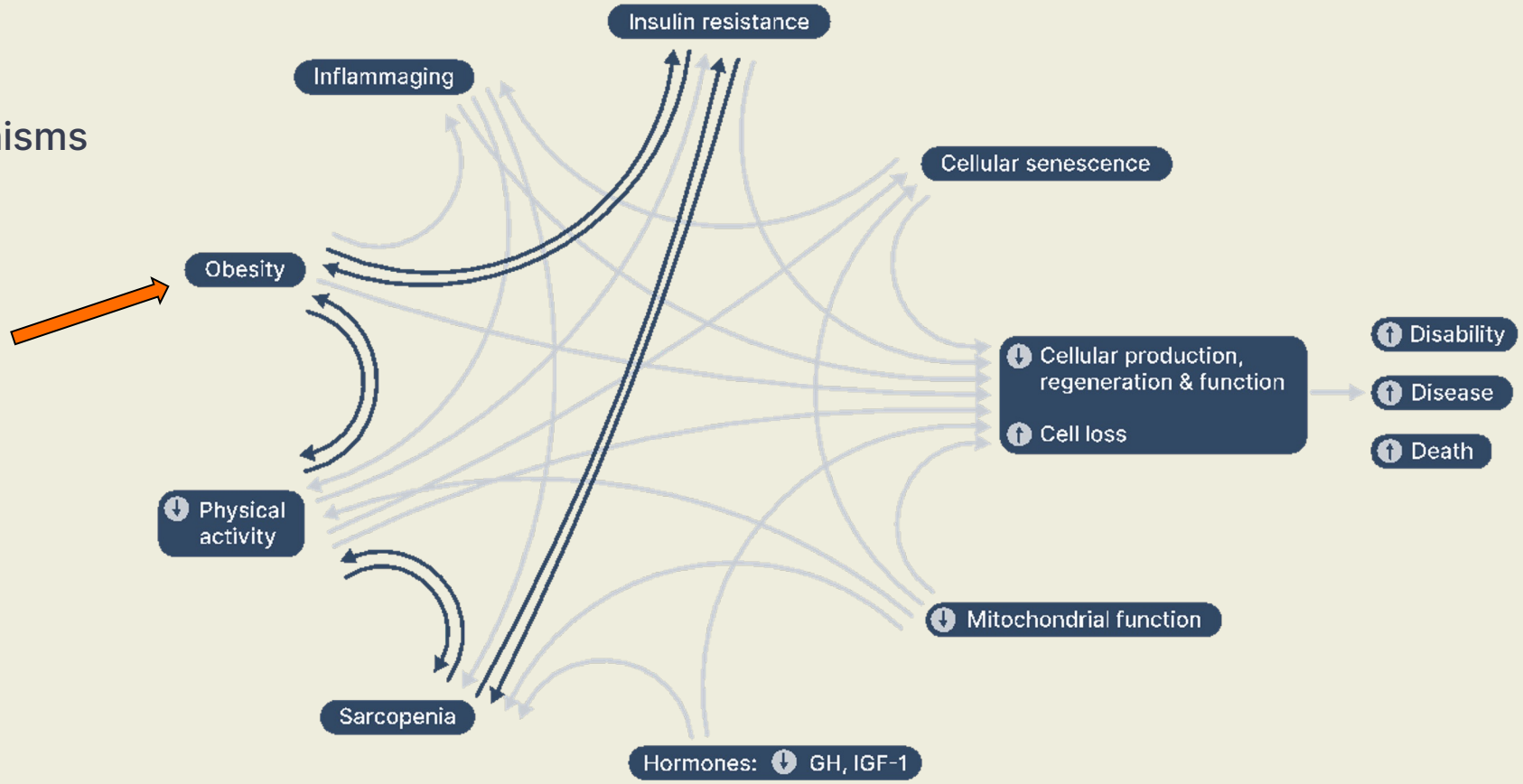

Shepherd M. Canine and Feline Obesity Management. Vet Clin North Am Small Anim Pract. 2021 May;51(3):653-667

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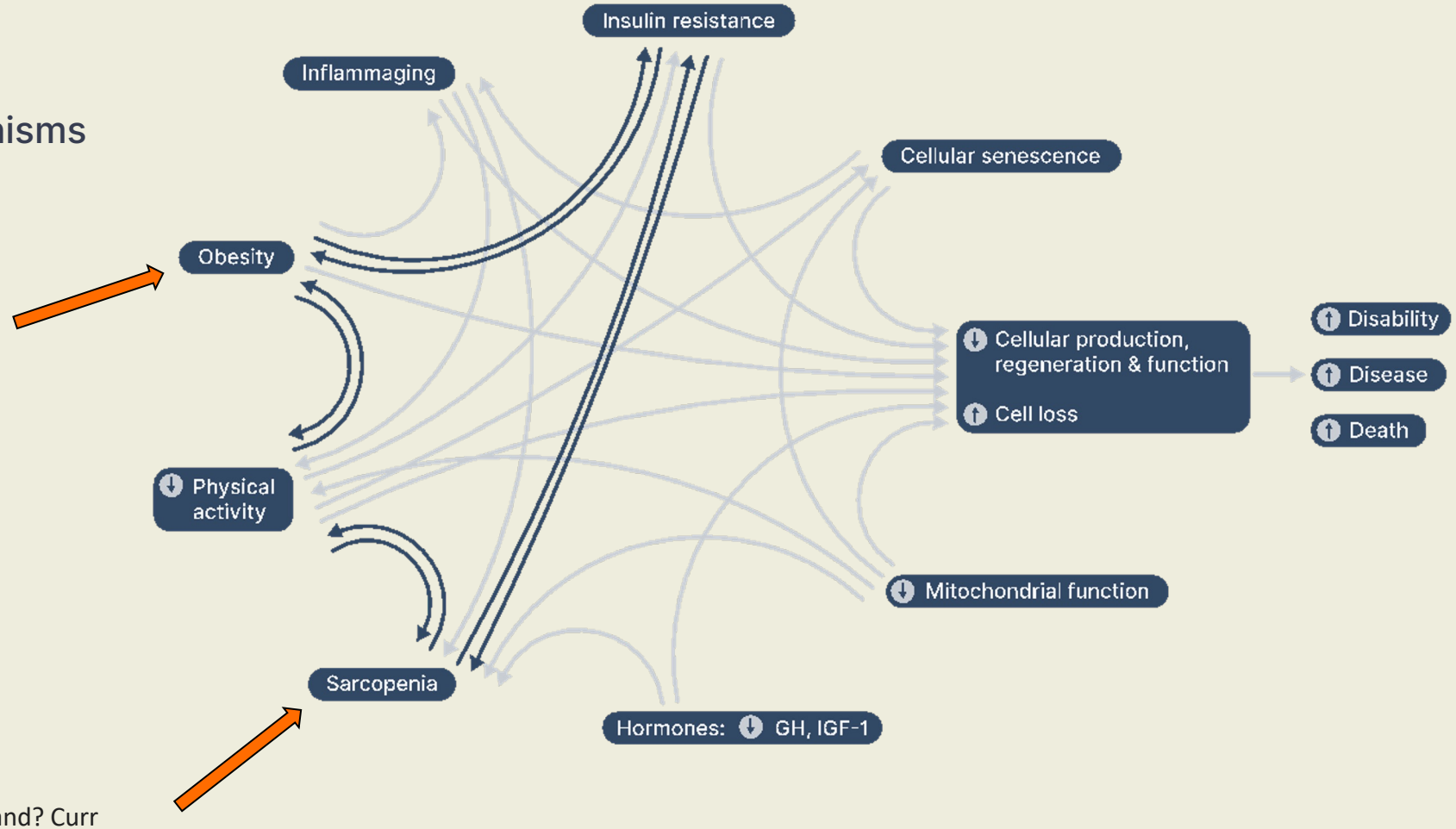

Woo J. Nutritional interventions in sarcopenia: where do we stand? Curr Opin Clin Nutr Metab Care. 2018 Jan;21(1):19-23.

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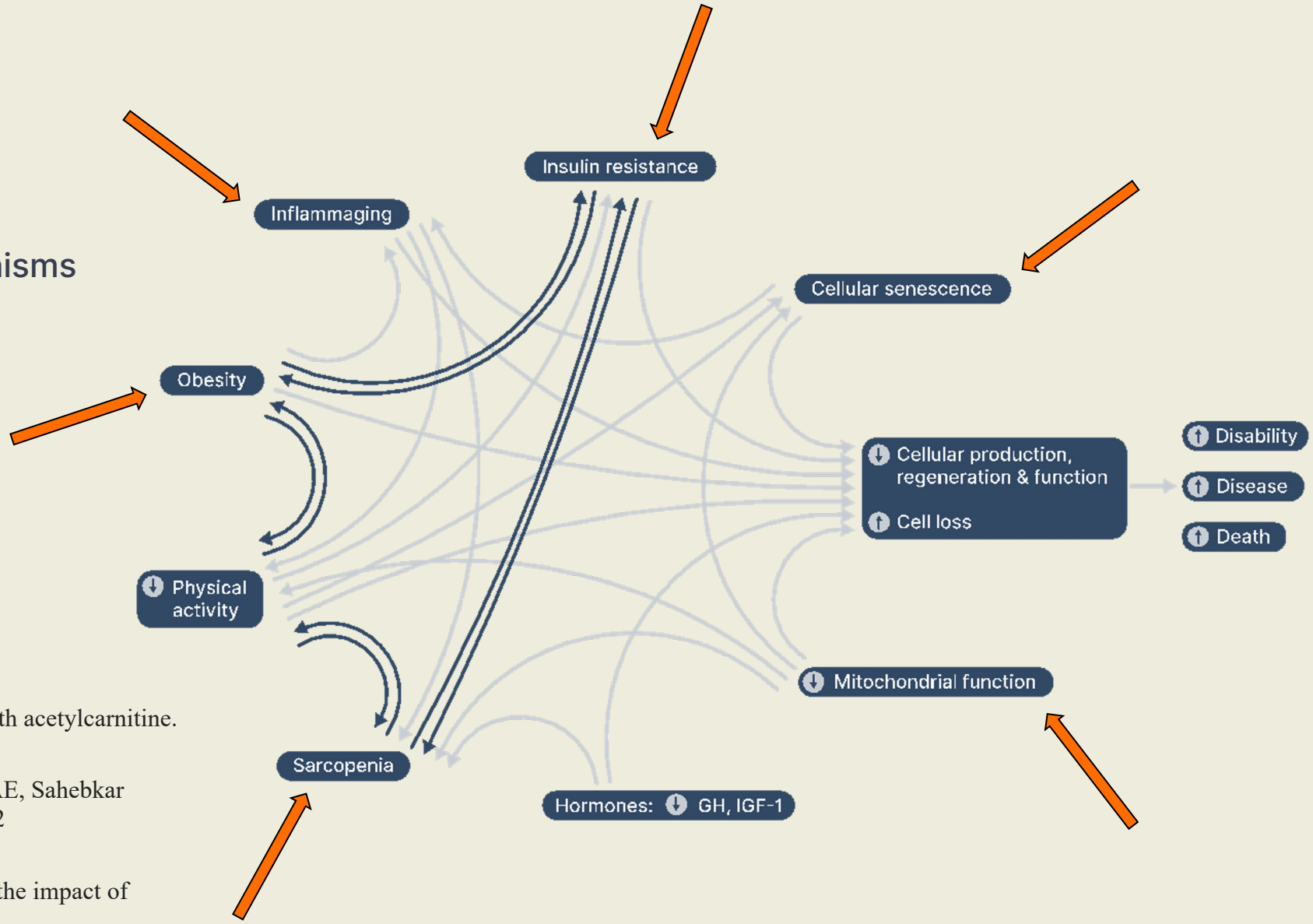

Ames BN, Liu J. Delaying the mitochondrial decay of aging with acetylcarnitine. Ann N Y Acad Sci. 2004 Nov;1033:108-16.

Di Giosia P, Stamerra CA, Giorgini P, Jamialahamdi T, Butler AE, Sahebkar A. The role of nutrition in inflammaging. Ageing Res Rev. 2022 May;77:101596.

Maduro AT, Luís C, Soares R. Ageing, cellular senescence and the impact of diet: an overview. Porto Biomed J. 2021 Feb 11;6(1):e120.

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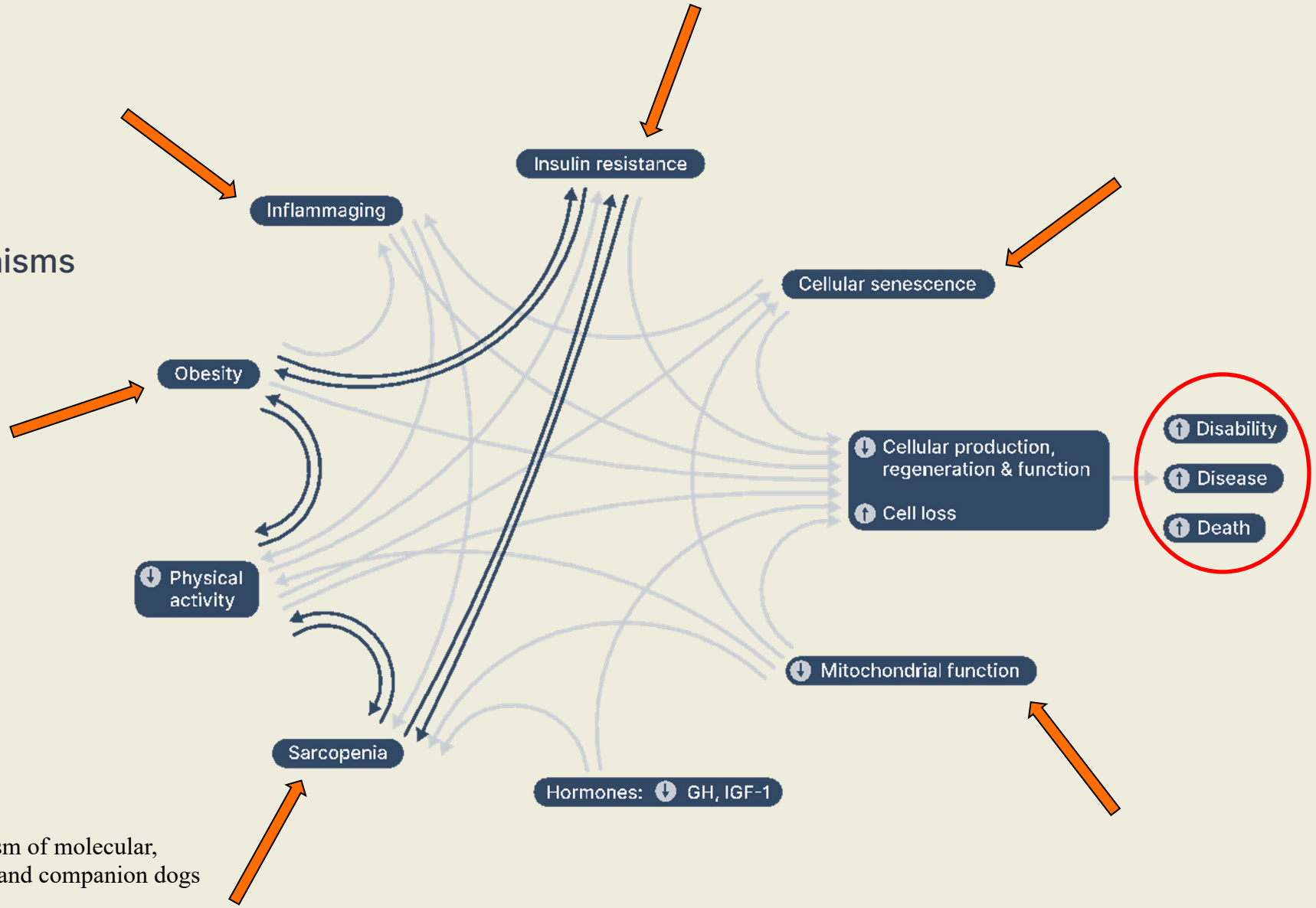

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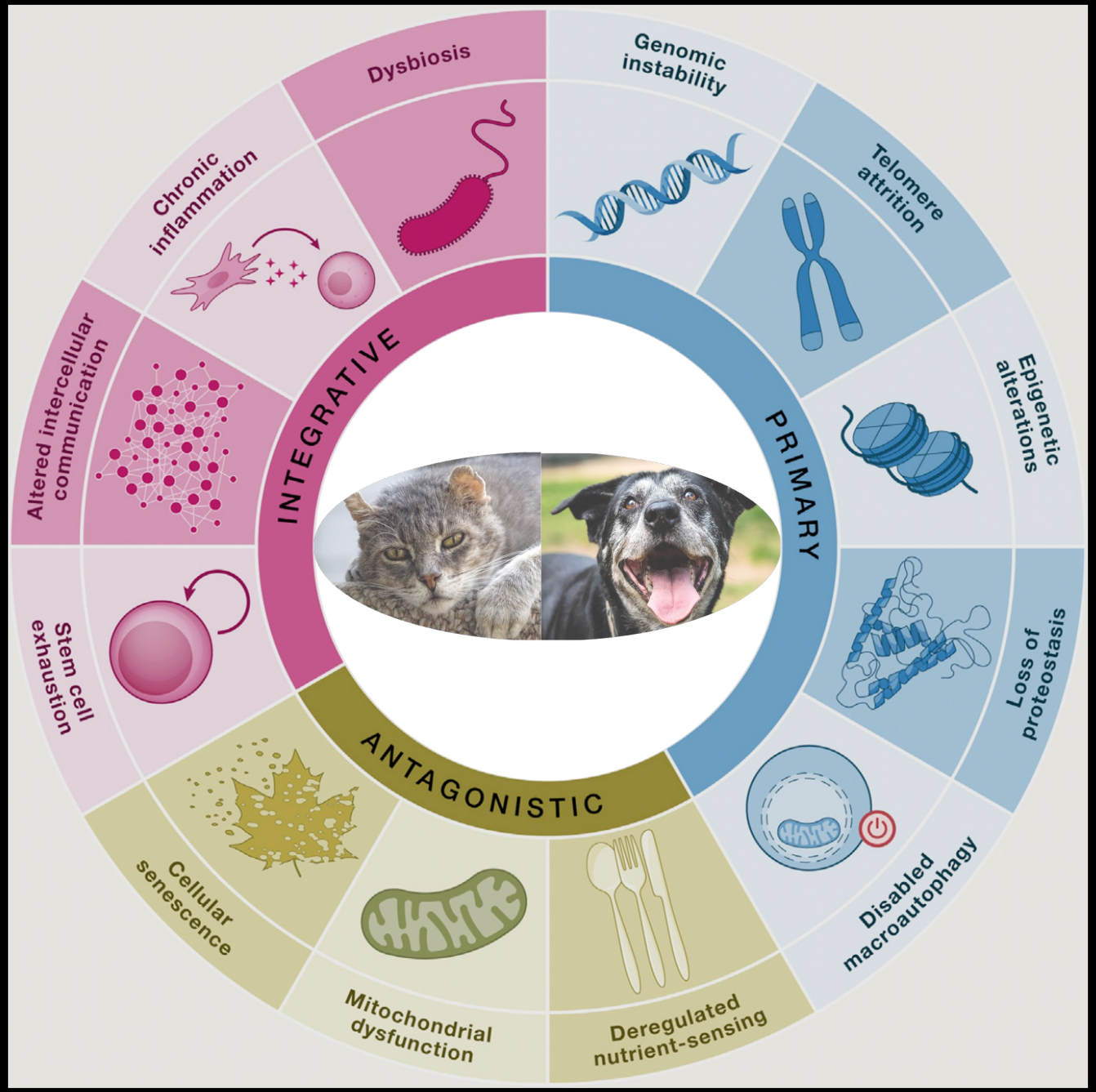
Dysbiosis
Genomic instability
Telomere attrition
Epigenetic alterations
Loss of proteostasis
Disabled macroautophagy
Deregulated nutrient-sensing
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Altered intercellular communication
Chronic inflammation
INTEGRATIVE
PRIMARY
ANTAGONISTIC


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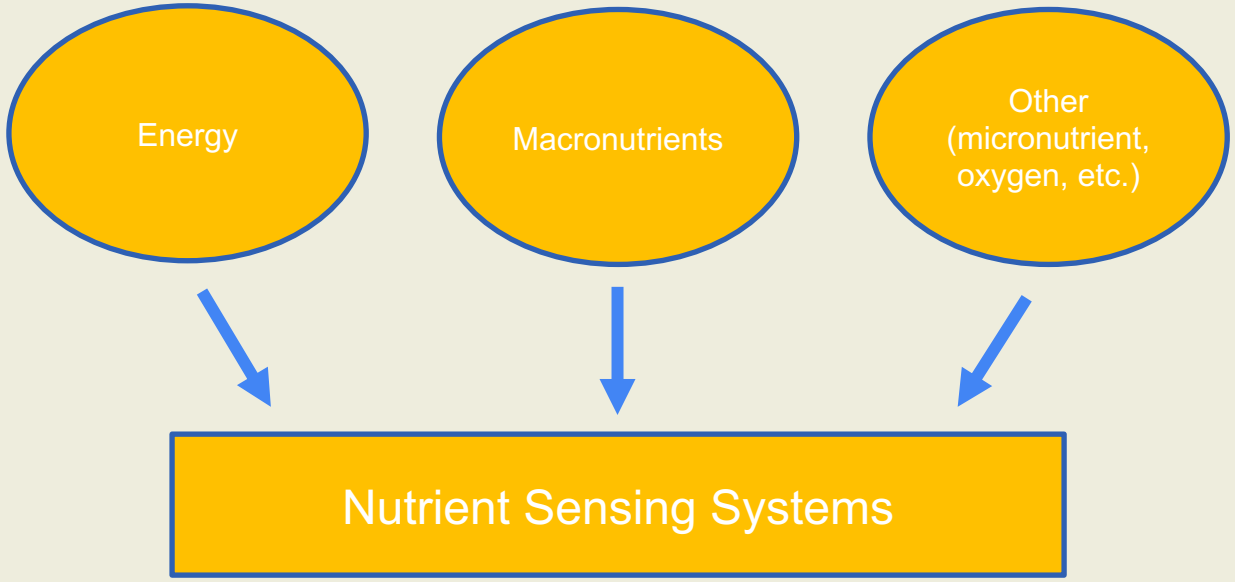
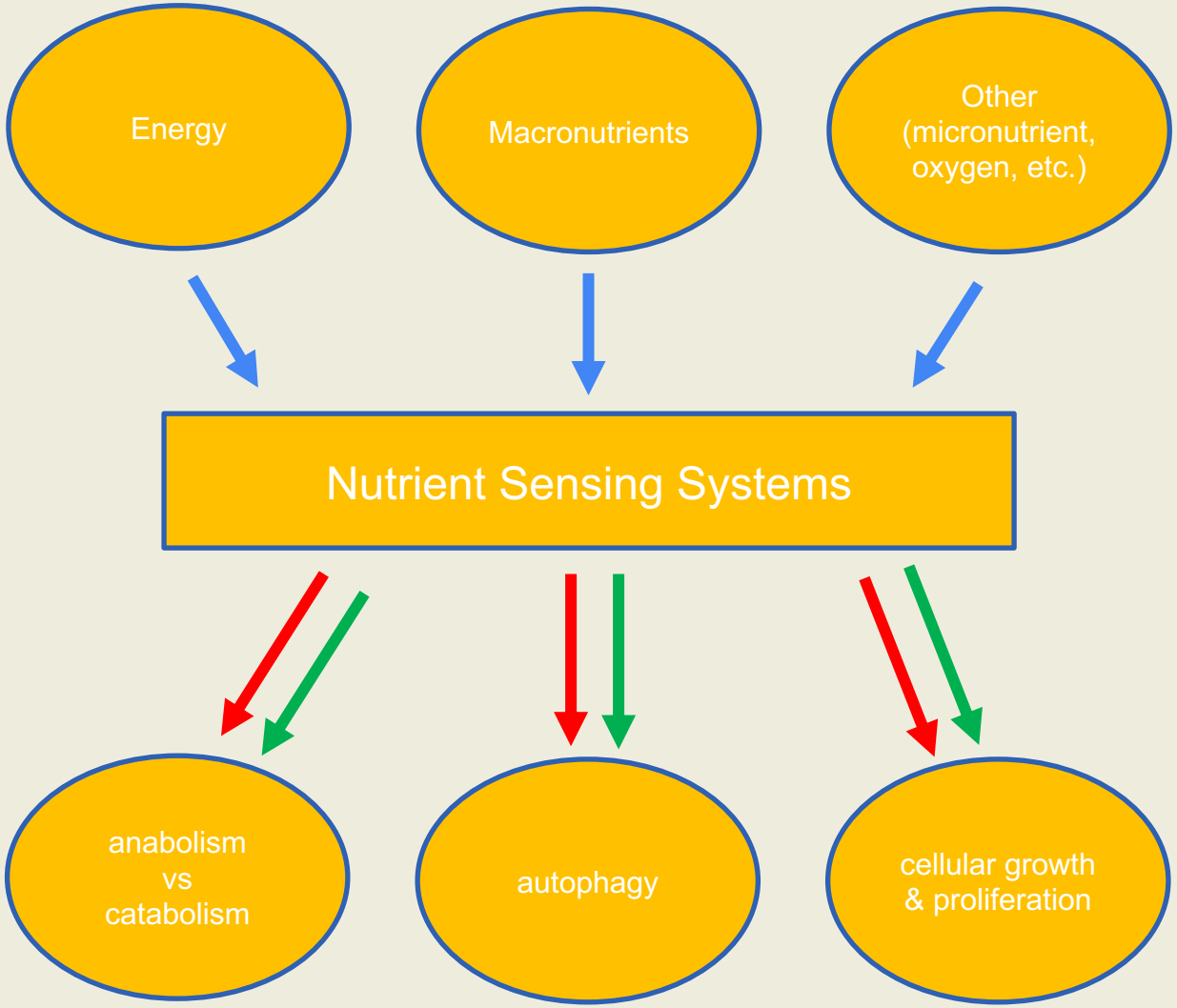


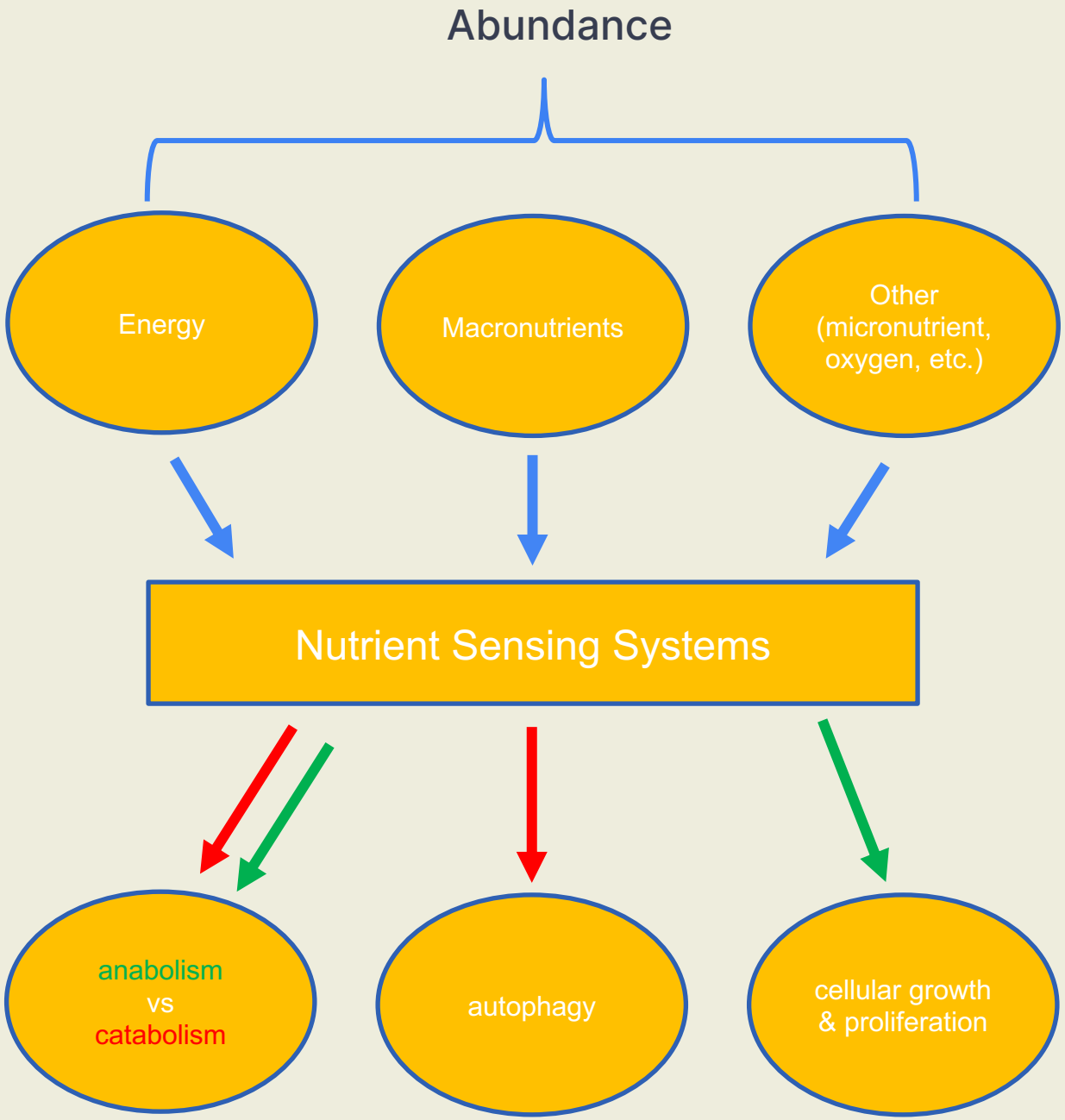
Nutrient Sensing & Aging

- Monitoring
  - energy
  - macronutrients
  - other



Nutrient Sensing & Aging

- **Monitoring**
  - energy
  - macronutrients
  - other
- **Adjusting**
  - anabolism/catabolism
  - autophagy
  - cellular growth & proliferation



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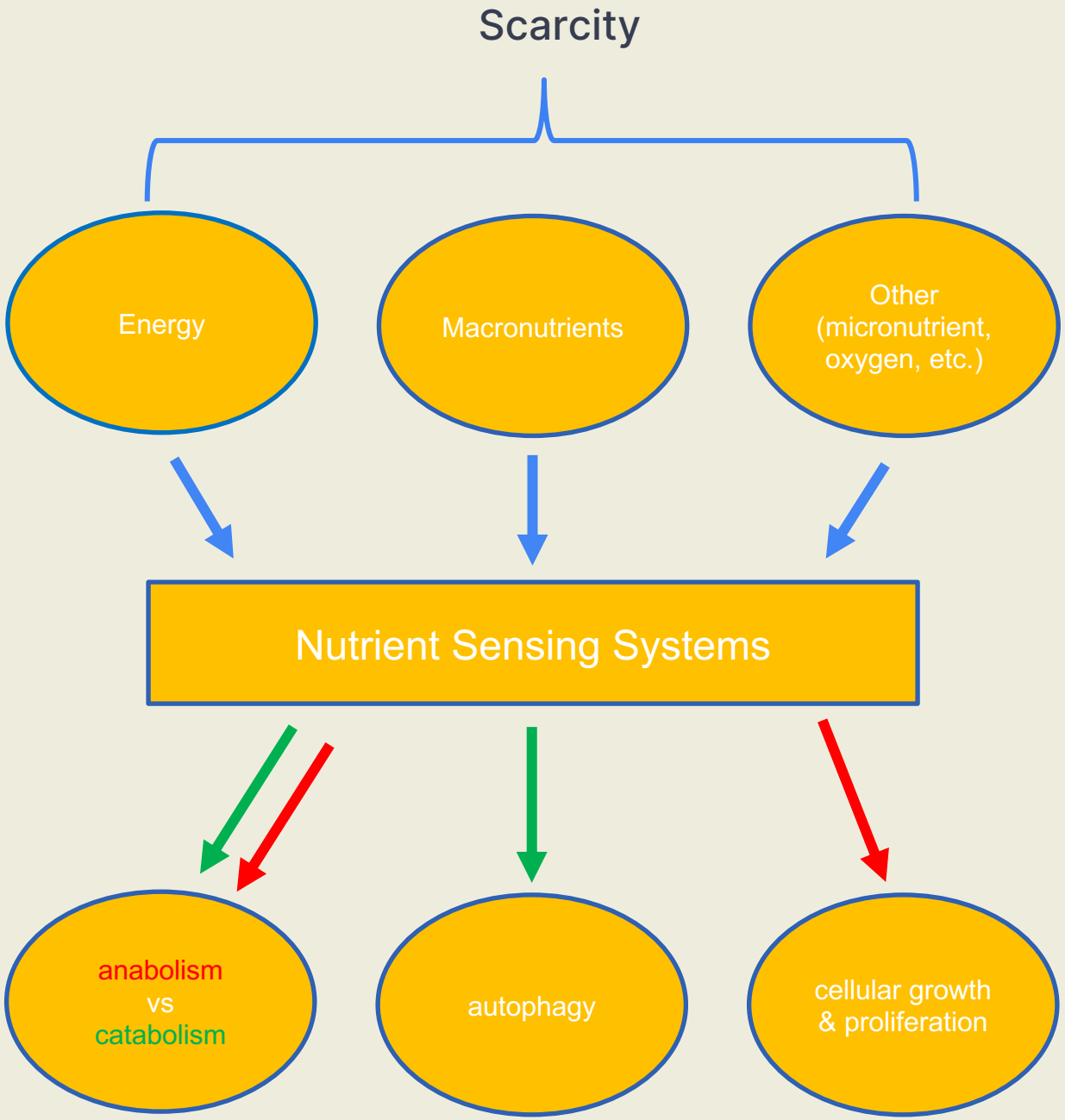

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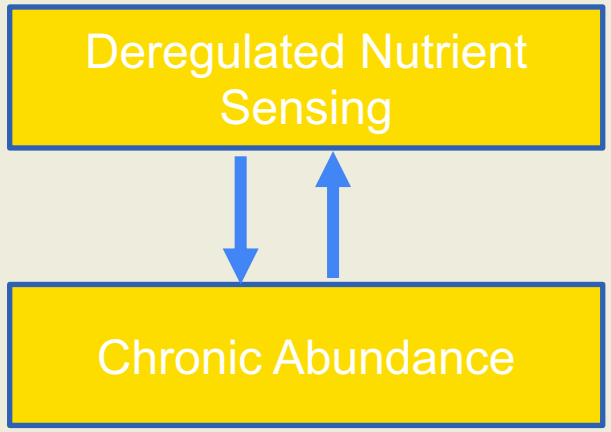
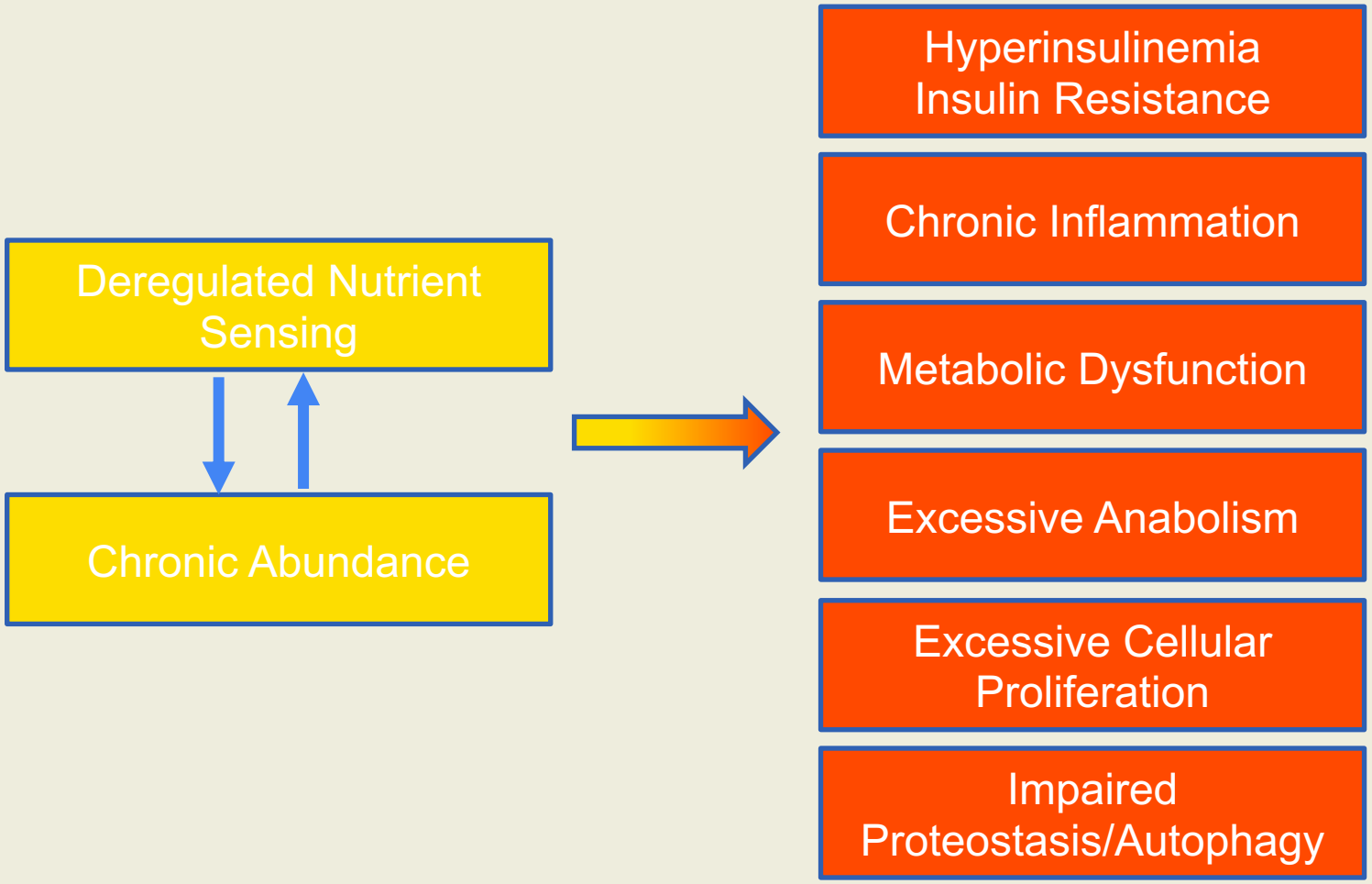
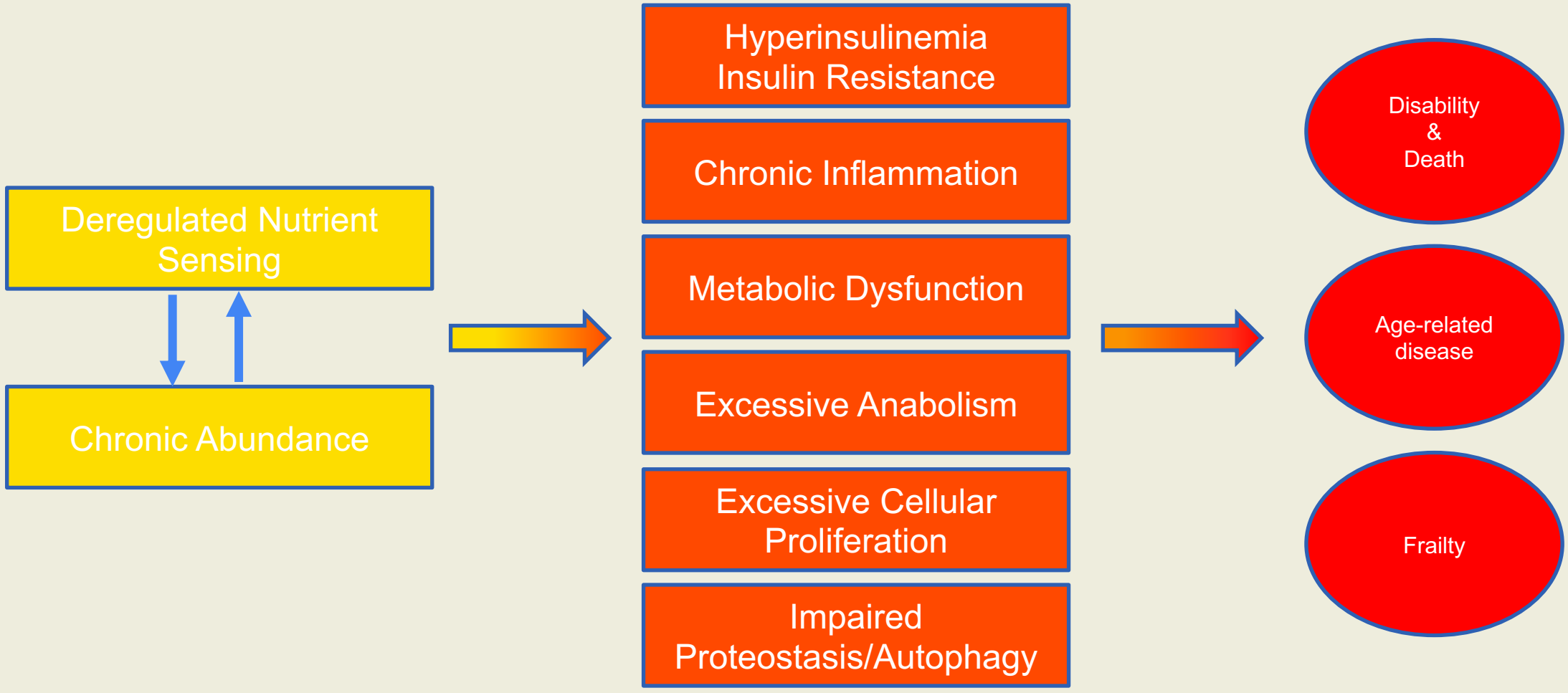

Deregulated Nutrient Sensing
Chronic Abundance


Deregulated Nutrient Sensing
Chronic Abundance
Hyperinsulinemia
Insulin Resistance
Chronic Inflammation
Metabolic Dysfunction
Excessive Anabolism
Excessive Cellular Proliferation
Impaired Proteostasis/Autophagy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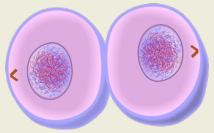
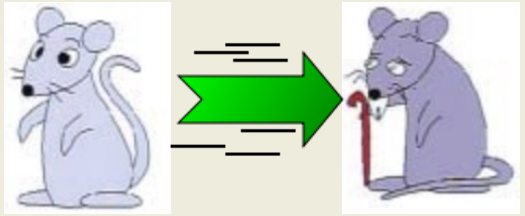
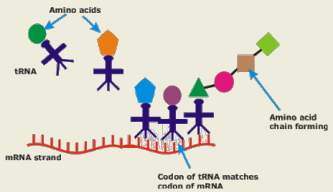
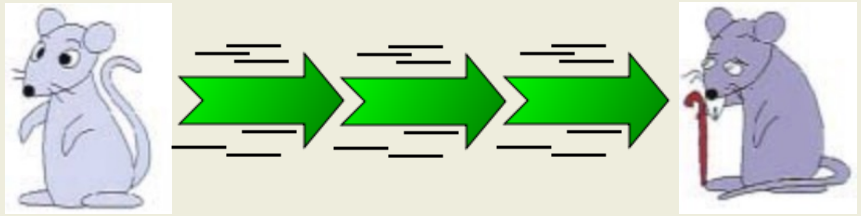
Chronic Abundance
Hyperinsulinemia Insulin Resistance
Chronic Inflammation
Metabolic Dysfunction
Excessive Anabolism
Excessive Cellular Proliferation
Impaired Proteostasis/Autophagy
Disability & Death
Age-related disease
Frailty


Heroes & Villains

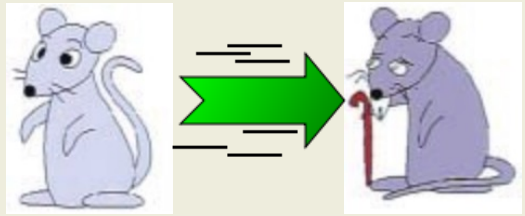
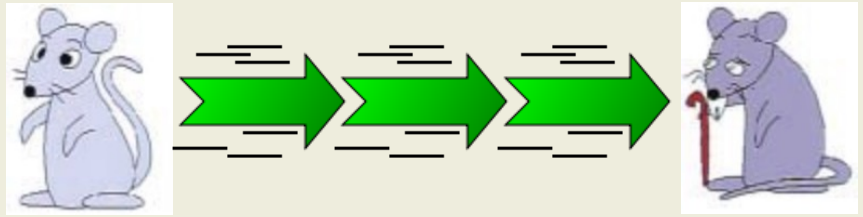
Villains

Regulator	Activity	Lifespan Effects
mTORC1 (mechanistic target of rapamycin)		
GH/IGF-1 (growth hormone/insulin-like growth factor 1)		
PI3K/AKT (protein kinases)		

Villains

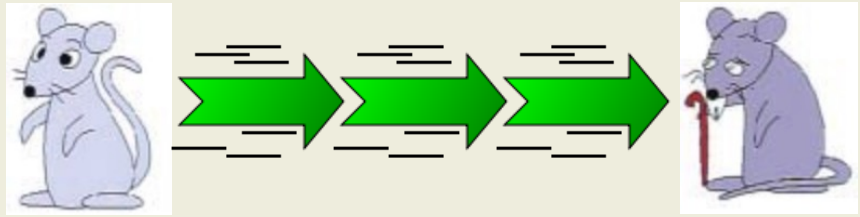
Regulator	Activity	Lifespan Effects
mTORC1 (mechanistic target of rapamycin)	↑ 	↑ mTORC1 
	↑ 	
	↑ 	↓ mTORC1 

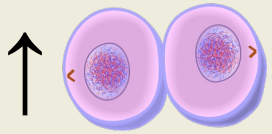
Villains

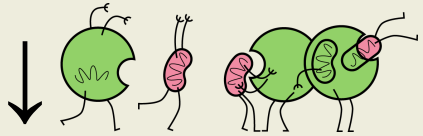
Regulator	Activity	Lifespan Effects
GH/IGF-1 (growth hormone/insulin-like growth factor 1)	↑ mTORC1	↑ GH/IGF-1
	↑ 	
	↓ FOXO	↓ GH/IGF-1
		

Villains

Regulator	Activity	Lifespan Effects
PI3K/AKT (protein kinases)	↑ mTORC1 ↓ FOXO	↓ PI3K/AKT



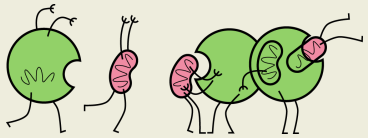
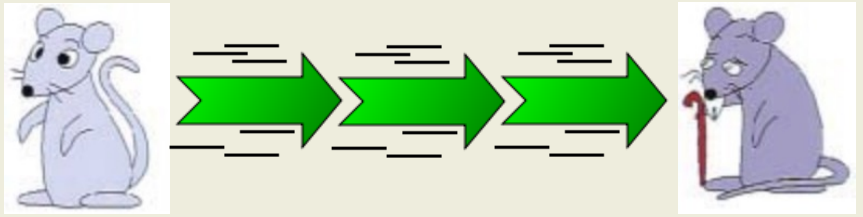




Heroes

Regulator	Activity	Lifespan Effects
AMPK (AMP-activated kinase)		
FOXO (forkhead box O transcription factors)		
FGF21 (fibroblast growth factor 21)		

Heroes

Regulator	Activity	Lifespan Effects
AMPK (AMP-activated kinase)	↓  ↑  ↓ mTORC1 ↑ FOXO	↑ AMPK 

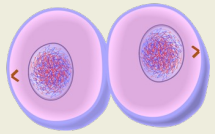
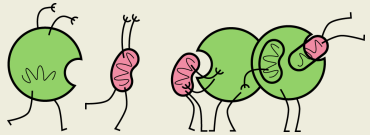
Heroes

Regulator

FOXO
(forkhead box O transcription factors)

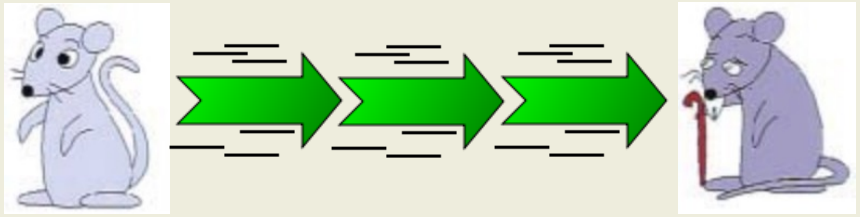
Activity

↓ mTORC1

- Nutritional stress response
- Energy metabolism
- 
- 

Lifespan Effects

↑ FOXO



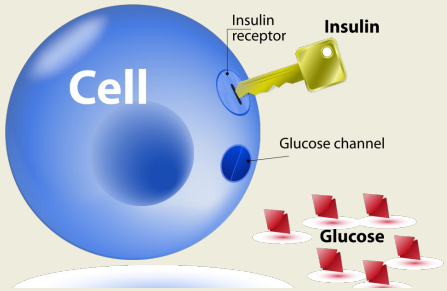
Heroes

Regulator

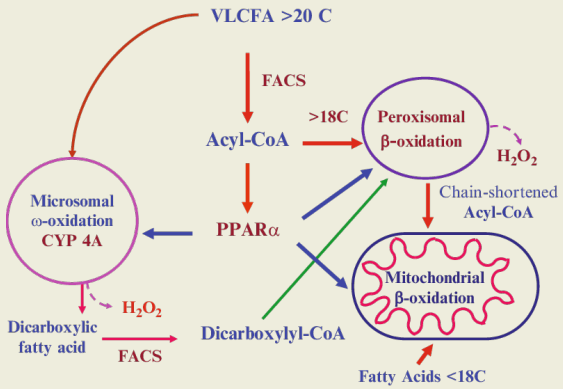
FGF21
(fibroblast growth factor 21)

Activity

↑



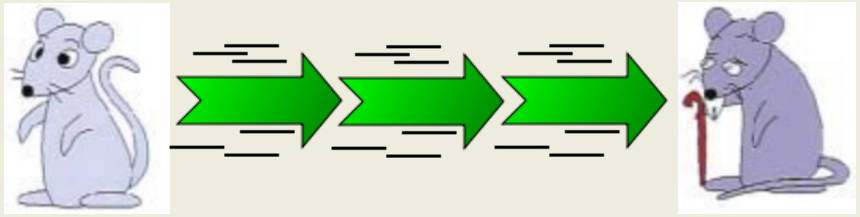
↑



↓ GH/IGF-1

Lifespan Effects

↑ FGF21



Villains

mTORC1

Villains

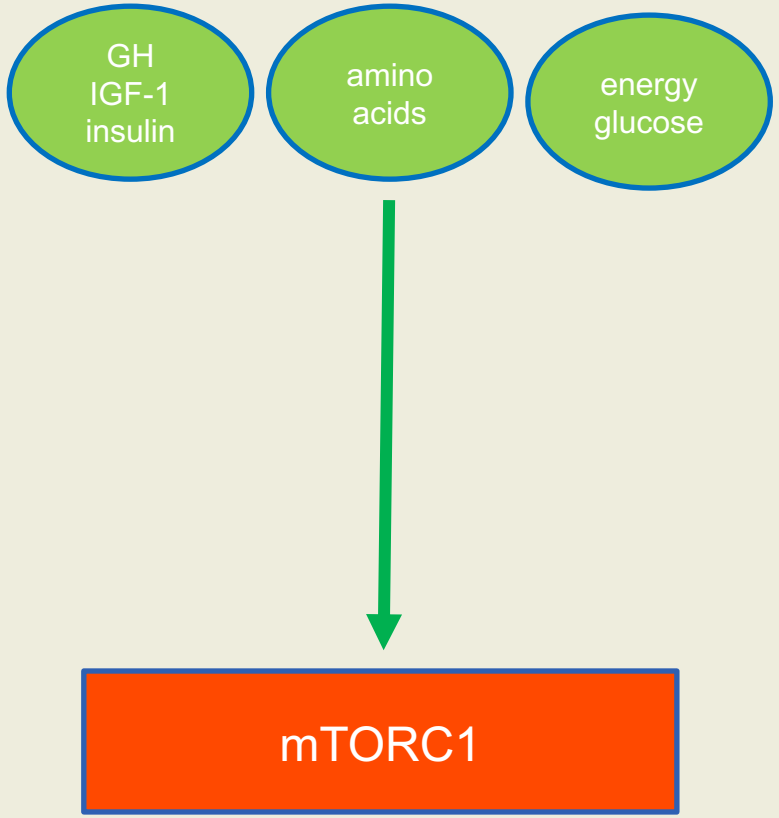
GH
IGF-1
insulin

amino
acids

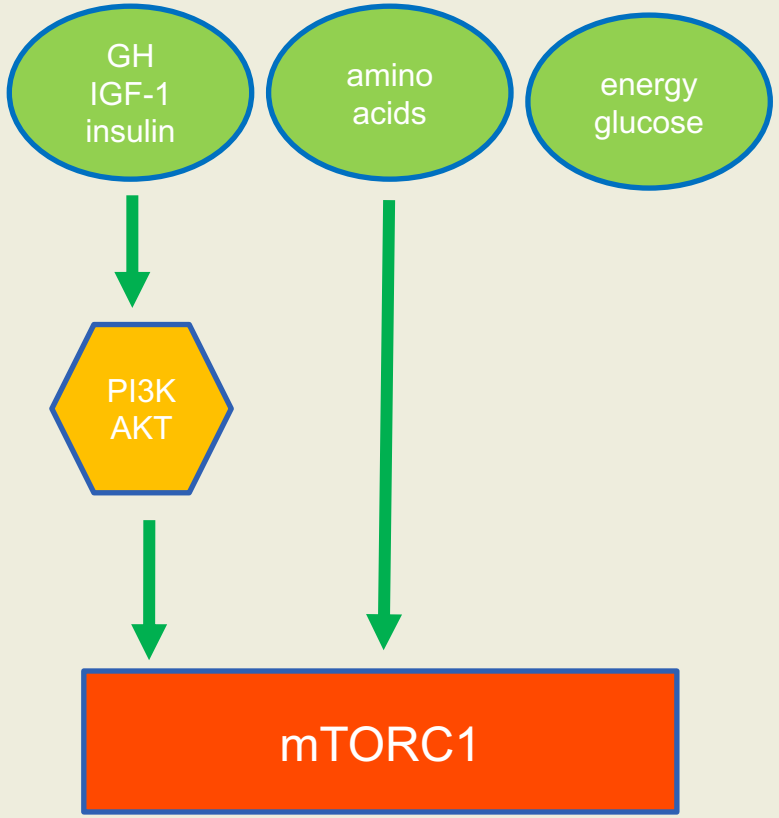
energy
glucose

mTORC1

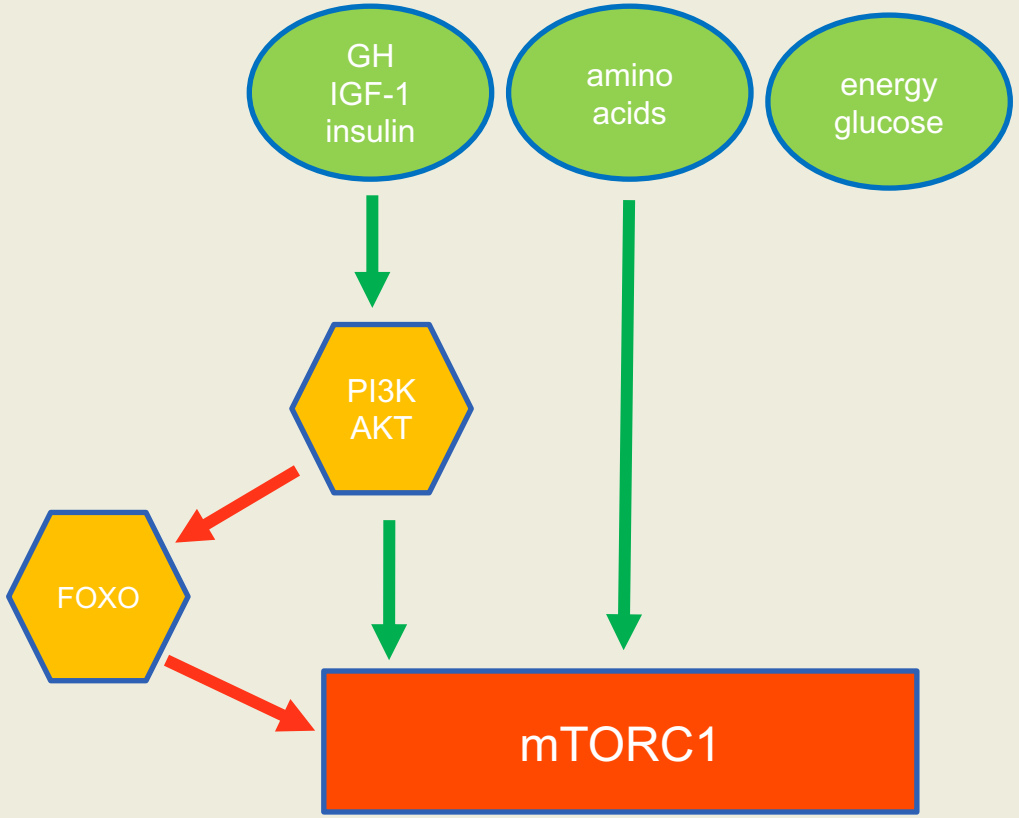
Villains

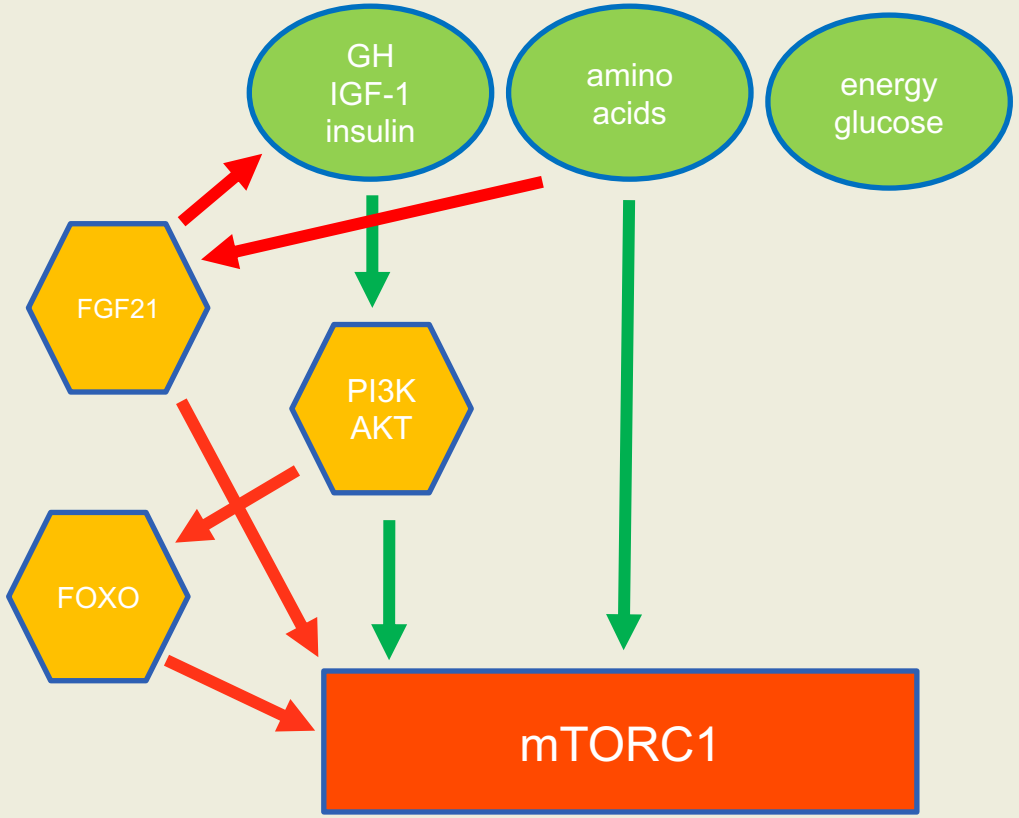


Villains



Villains


GH
IGF-1
insulin
amino
acids
energy
glucose
PI3K
AKT
FOXO
mTORC1


GH
IGF-1
insulin
amino
acids
energy
glucose
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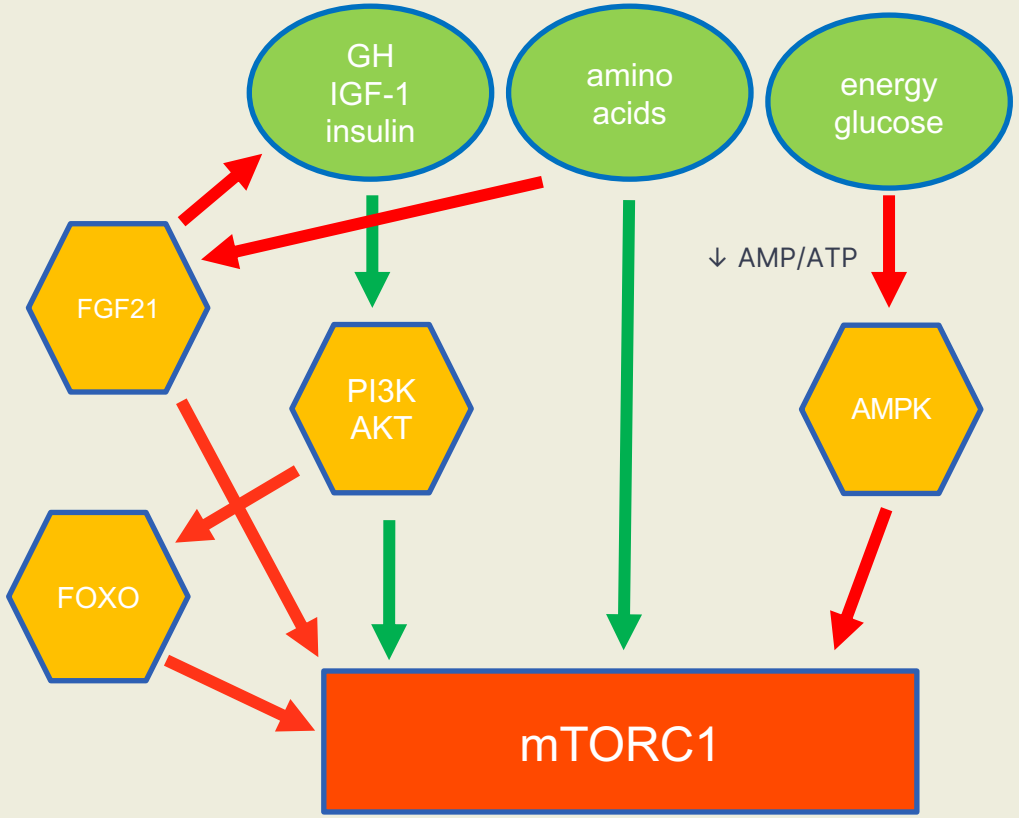
Villains


GH
IGF-1
insulin
amino
acids
energy
glucose
↓ AMP/ATP
FGF21
PI3K
AKT
AMPK
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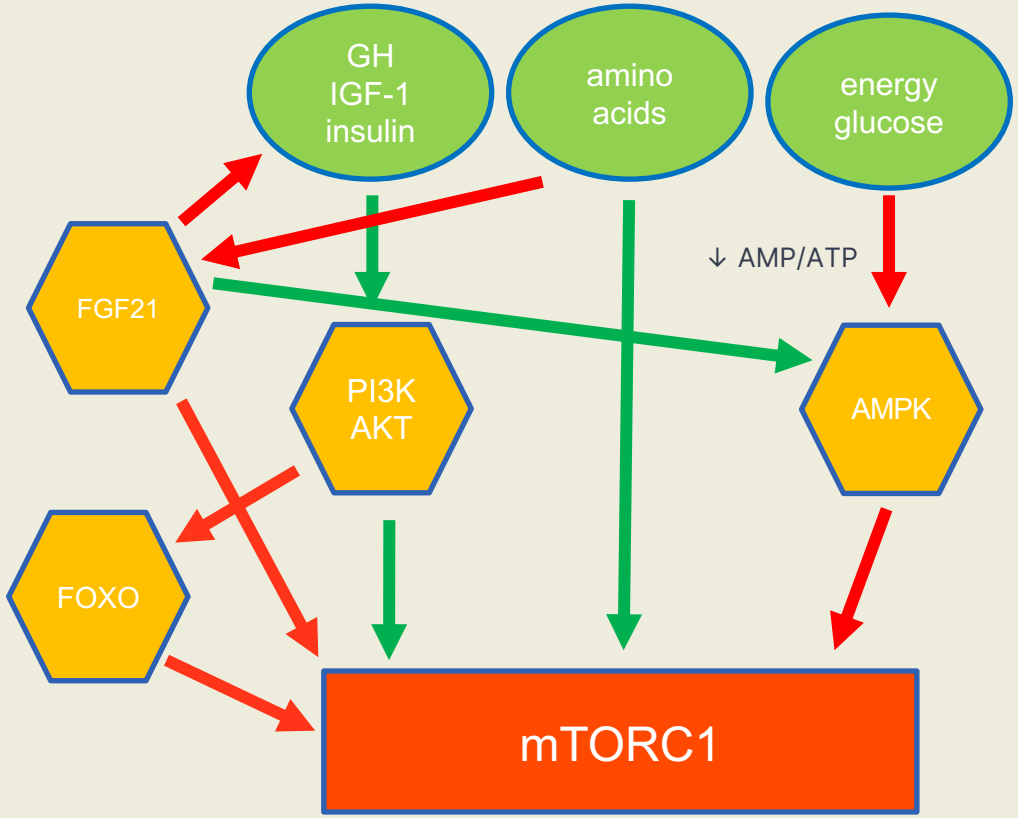
Villains


GH
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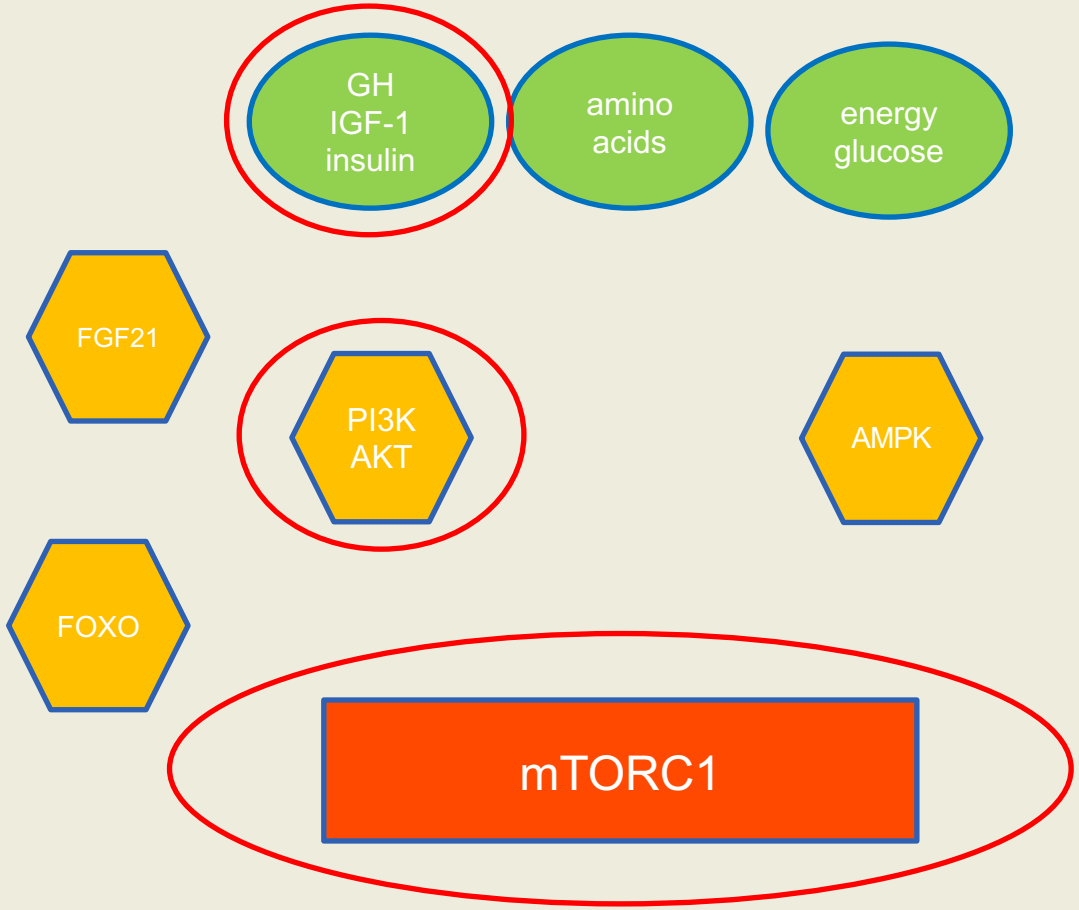
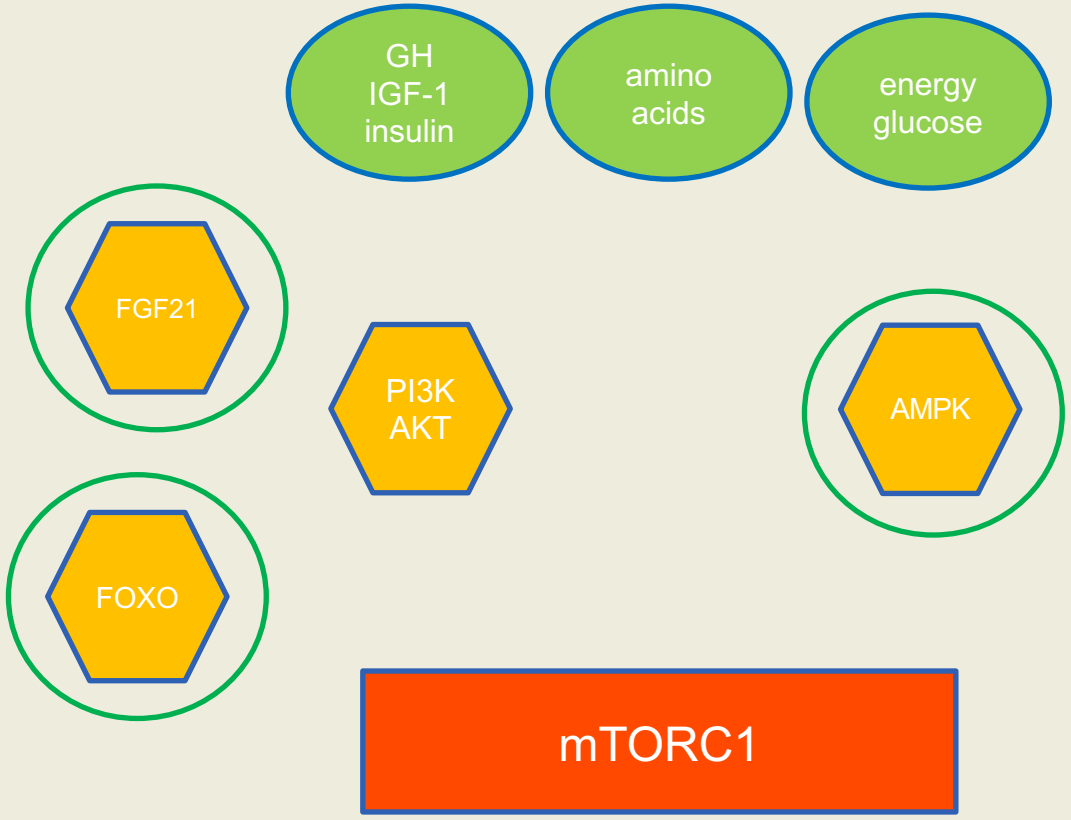

GH
IGF-1
insulin
amino
acids
energy
glucose
FGF21
PI3K
AKT
AMPK
FOXO
mTORC1

Heroes


GH
IGF-1
insulin
amino
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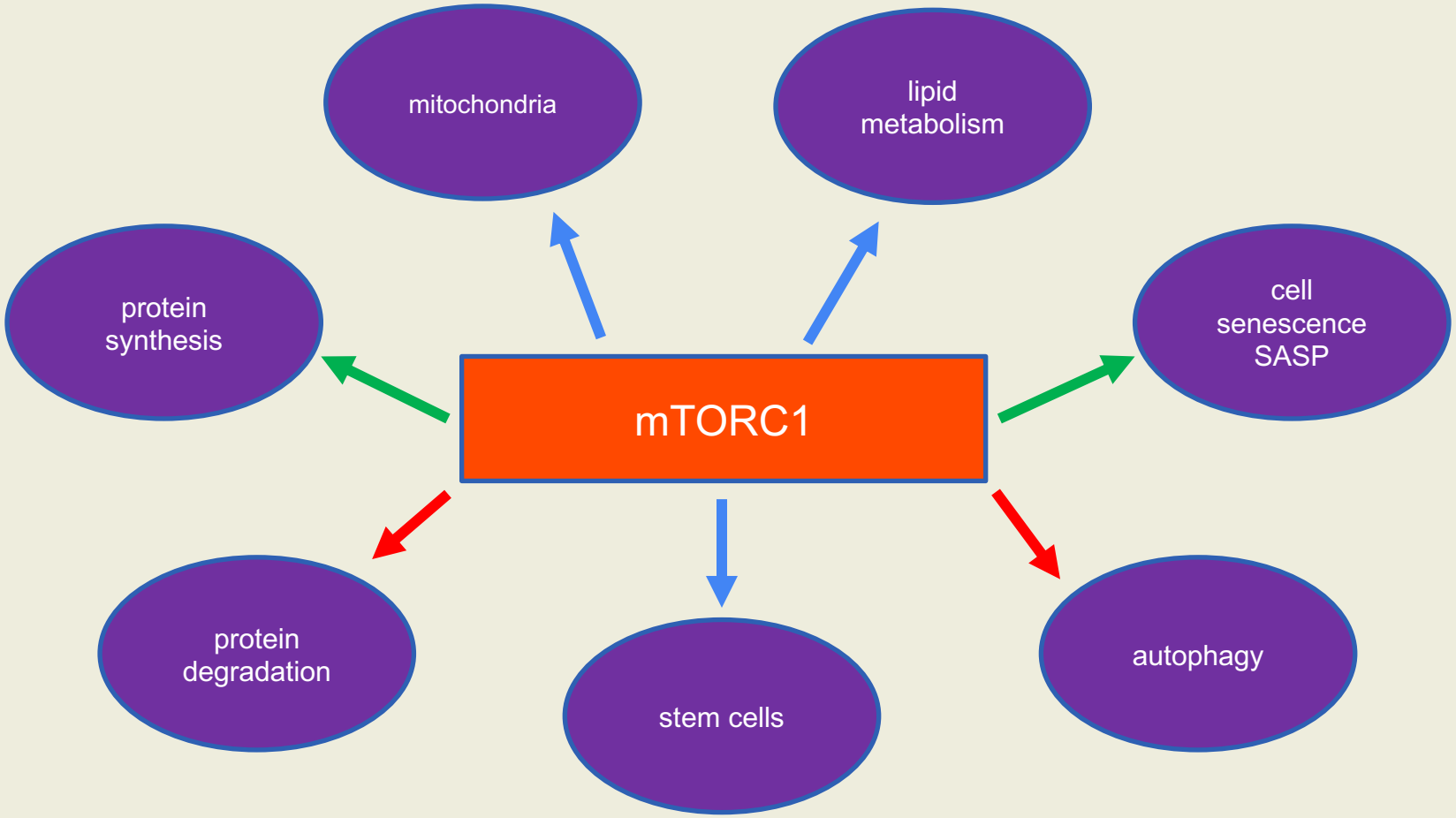
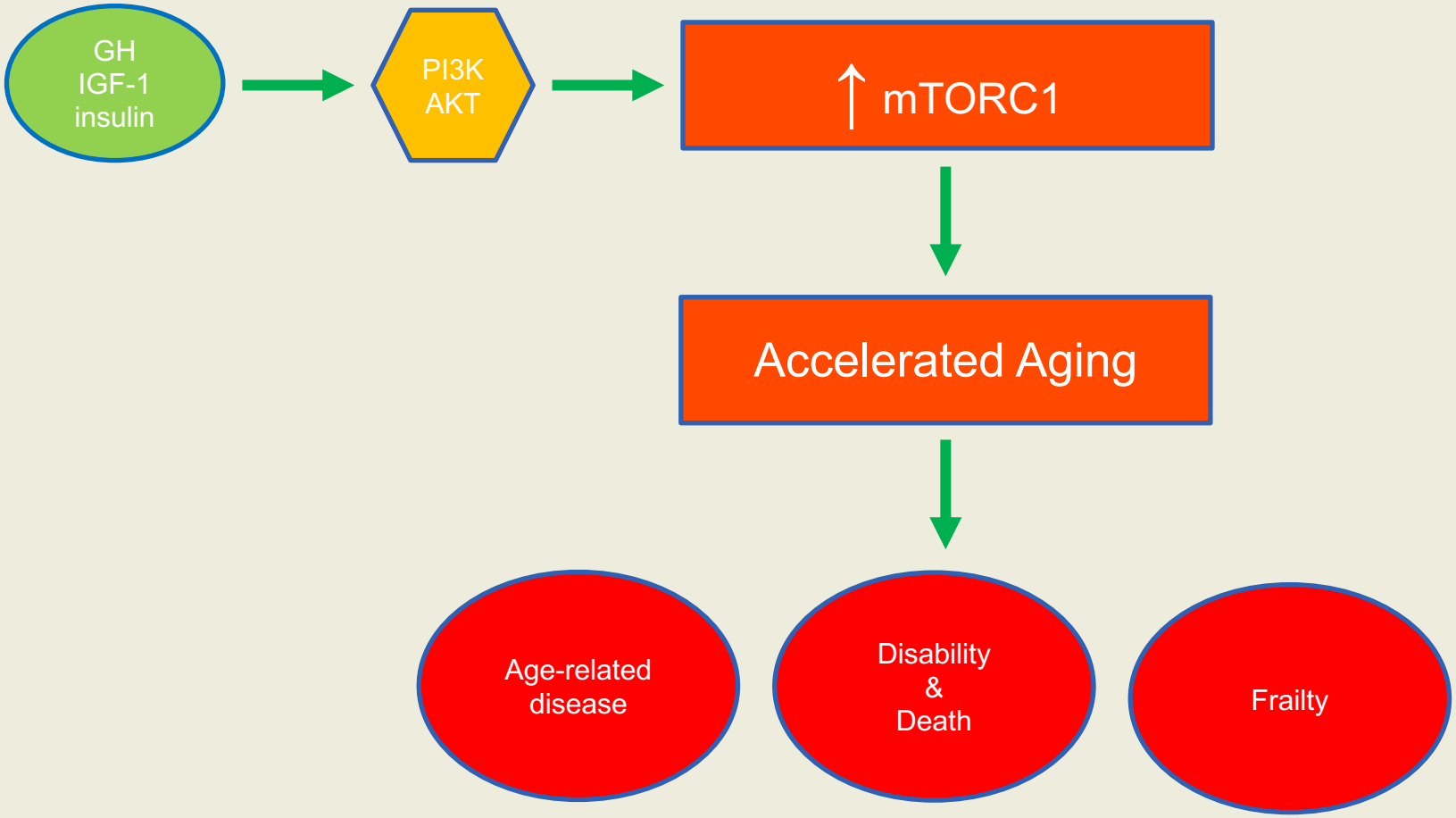
mTORC1

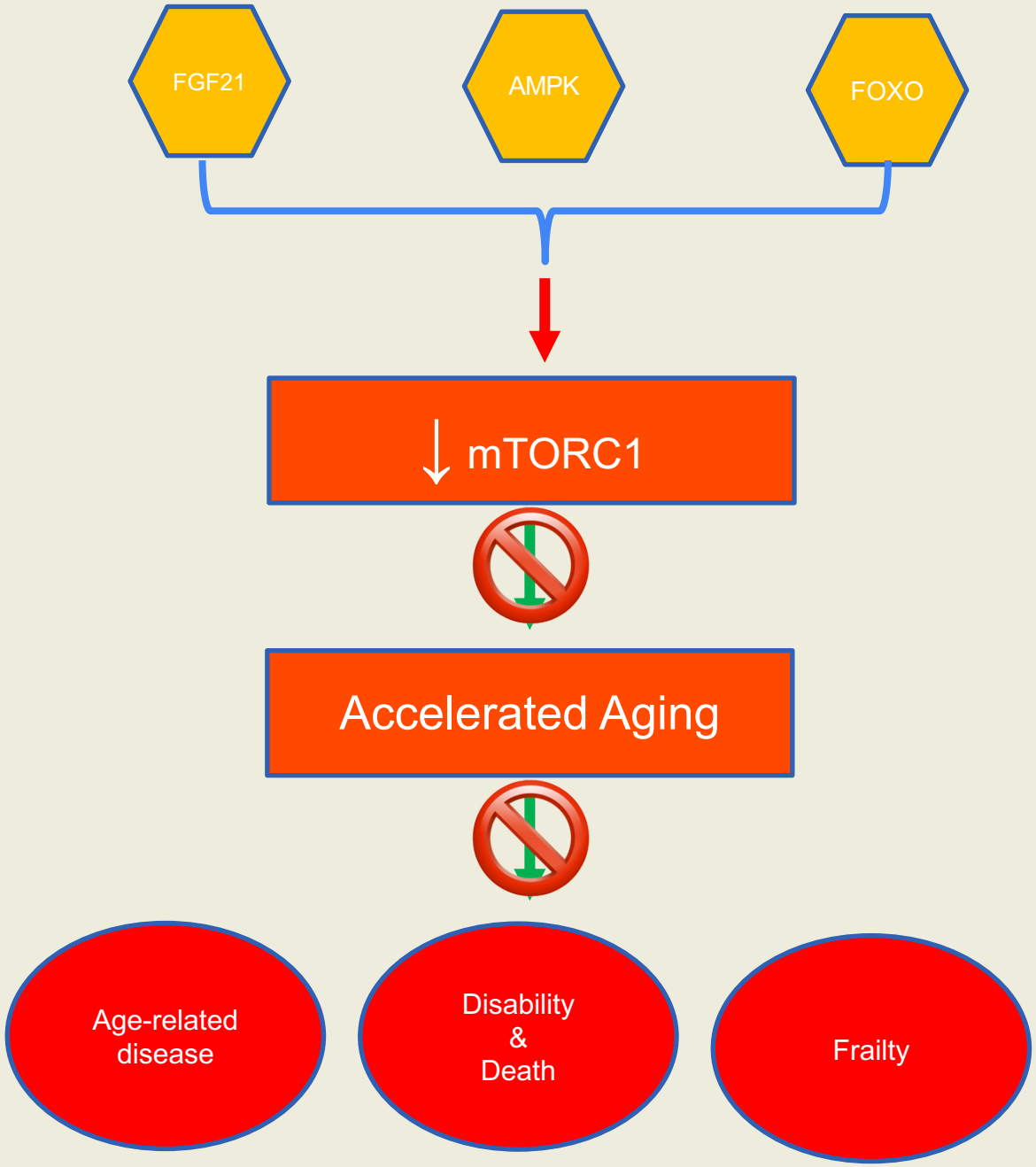
Villains


mitochondria
lipid metabolism
protein synthesis
cell senescence SASP
mTORC1
protein degradation
stem cells
autophagy

Villains


GH
IGF-1
insulin
PI3K
AKT
↑ mTORC1
Accelerated Aging
Age-related disease
Disability & Death
Frailty

Heroes


FGF21
AMPK
FOXO
↓ mTORC1
Accelerated Aging
Age-related disease
Disability & Death
Frailty

Nutritional Interventions

Targeting Aging Mechanisms

- **Restrain the Villains**
  - mTORC1
  - PI3K/AKT
  - GH/IGF-1/insulin
- **Support the Heroes**
  - AMPK
  - FOXO
  - FGF21

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  - PI3K/AKT
  - GH/IGF-1/insulin
- **Support the Heroes**
  - AMPK
  - FOXO
  - FGF21

Dietary Intervention	Description	Lifespan Effect
Low calorie interventions		in mice
"Classic" CR	Daily reduction in calories, typically by 20 to 50%, without malnutrition. Macronutrient ratios are unchanged.	↑ ↑ ↑
CR without protein restriction	CR where protein content is modified so that only calories are reduced and protein intake is not changed.	↑ ↑ ↑
Intermittent Fasting (IF)	CR variant with at least one day of fasting between feedings. Many classic CR studies used intermittent fasting protocols where mice were fed 3 times per week.	↑ ↑ ↑
Fasting-Mimicking (FMD)	Cyclic CR where a low-calorie, ketogenic diet is provided during the restricted phase. In mice, FMD cycles are typically 3–4 days followed by 3 days of refeeding.	↑ ↑
Iso-caloric Diets		
Protein restriction (PR)	In mice and rats, isocaloric protein restriction has been reported to extend lifespan, but the effects appear to be much smaller than CR and may be sex-specific in mice*.	↑
Essential Amino Acid Restriction	Restriction of methionine, tryptophan, or branched chain amino acid content in the diet. Essential amino acid restriction in mice typically involves reducing methionine by about 80%, tryptophan by about 40%, or branched chain amino acids by about 67%. It remains unclear what extent these interventions share similar mechanisms.	↑

Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. Science. 2021 Nov 19;374(6570):eabe7365; Epub 2021 Nov 19.

→ Targeting Mechanisms of Aging

- Caloric Restriction
- Protein/Amino Acid Restriction
- Fasting/Fasting Mimicking Diets
- Pharmaceuticals

Caloric Restriction

- Restrict calories without malnutrition
  - 20%-40%

Caloric Restriction

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  - 20%-40%
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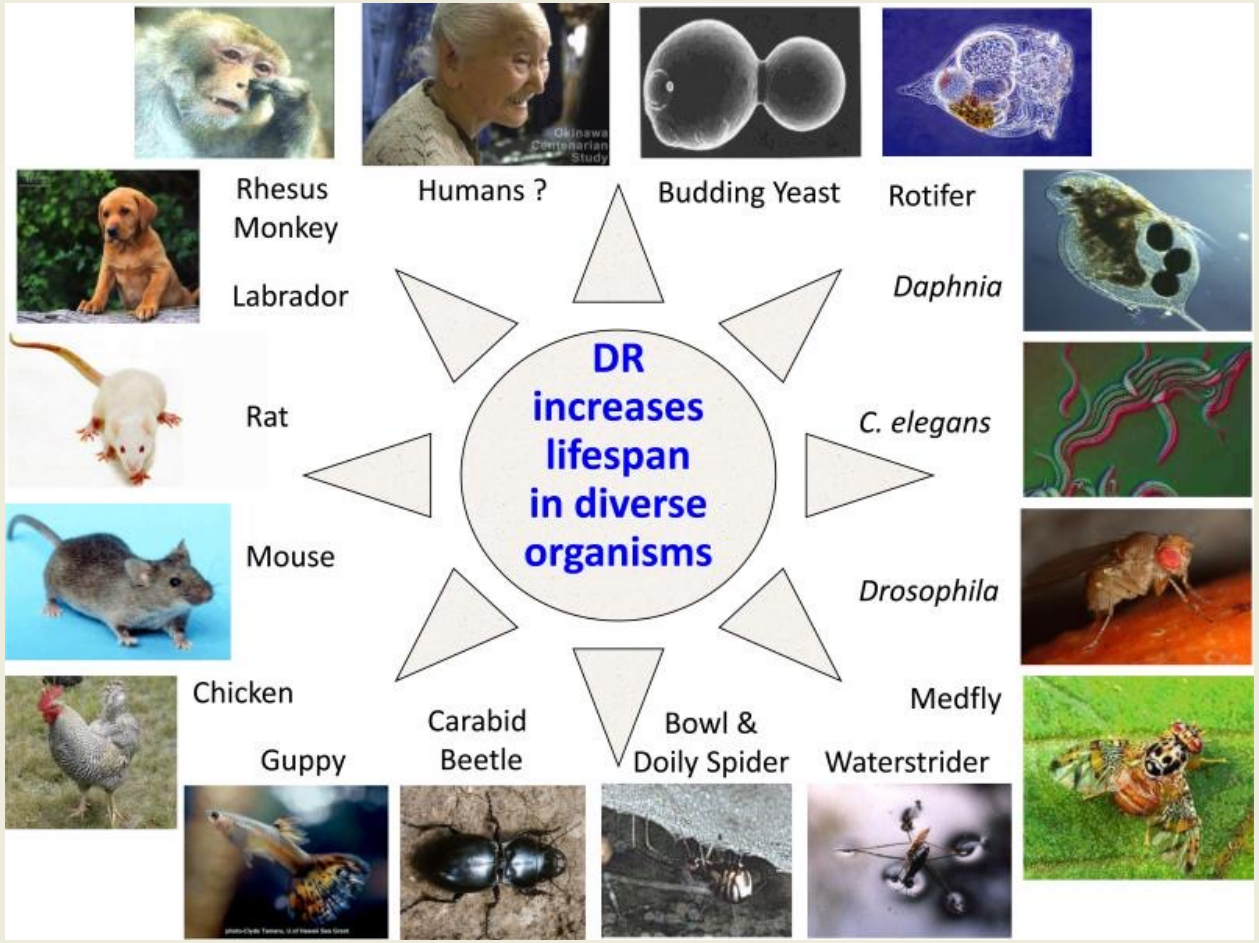
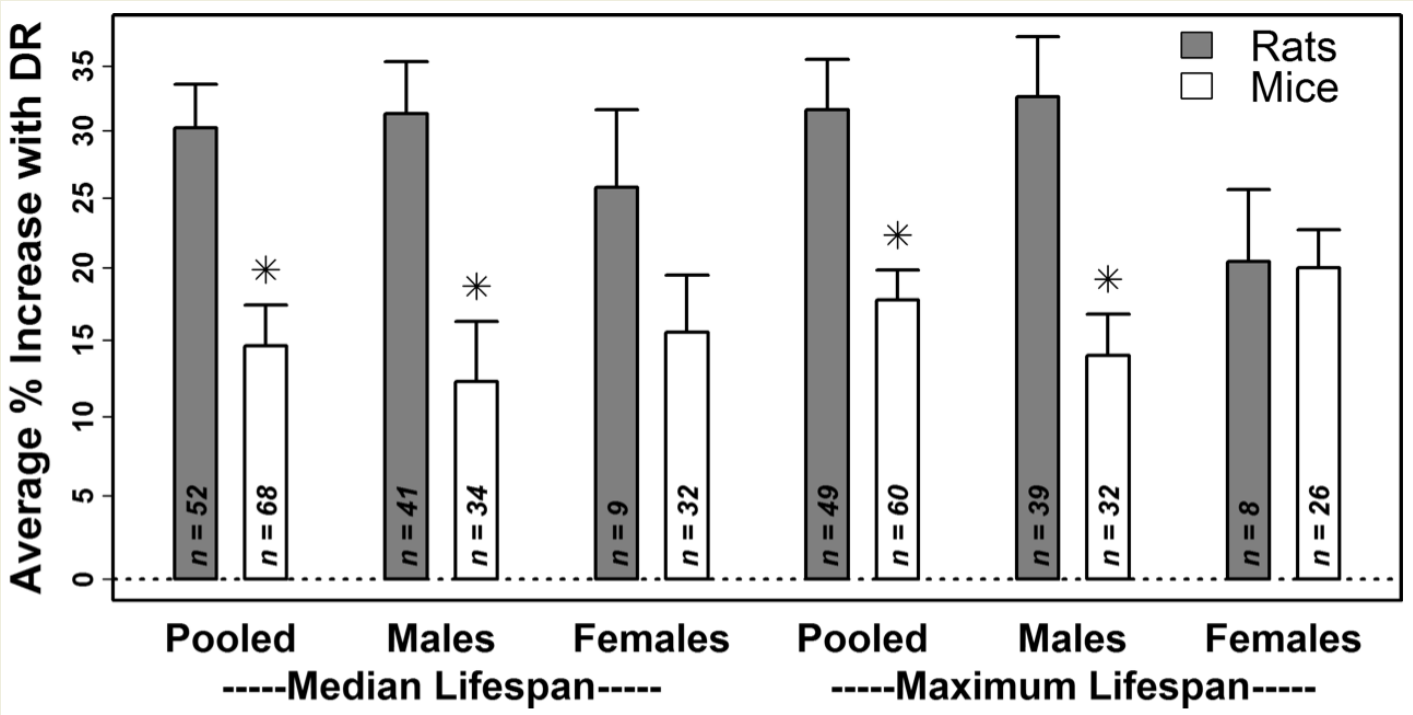


Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. Cell. 2015 Mar 26;161(1):106-118.

Caloric Restriction

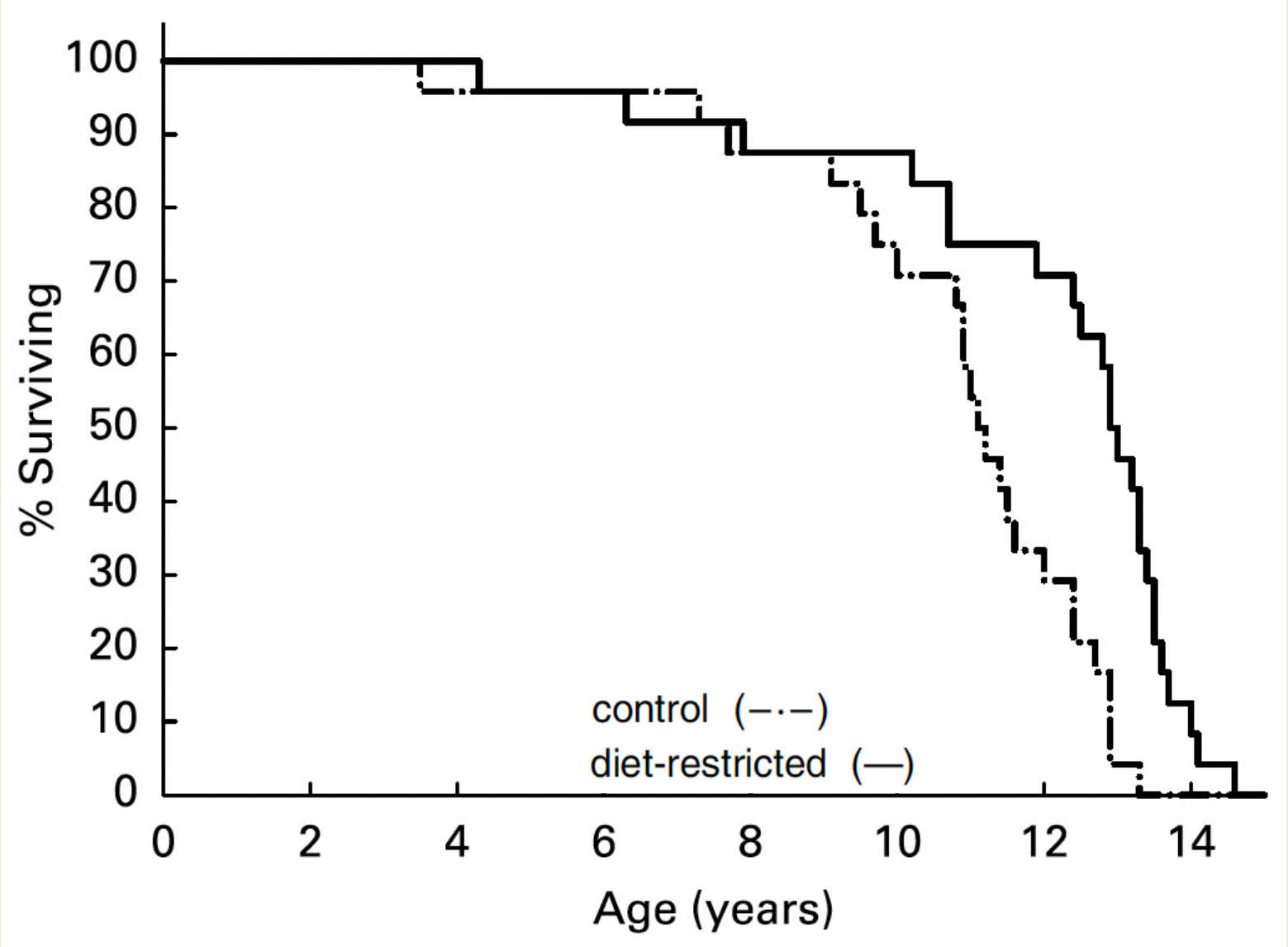
- Restrict calories without malnutrition
  - 20%-40%
- Extends lifespan (mostly)
  - Rats > mice
  - Inbred > wild-derived
  - Sex effects
  - Age of onset effects
  - Species differences
  - Husbandry, diet, etc...



Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. Ageing Res Rev. 2012 Apr;11(2):254-70.

Caloric Restriction

- Dogs
  - Lifespan (median and maximum)



Lawler DF, Larson BT, Ballam JM, Smith GK, Biery DN, Evans RH, Greeley EH, Segre M, Stowe HD, Kealy RD. Diet restriction and ageing in the dog: major observations over two decades. Br J Nutr. 2008 Apr;99(4):793-805.

Caloric Restriction

- Dogs
  - Lifespan (median and maximum)
  - Age-associated disease

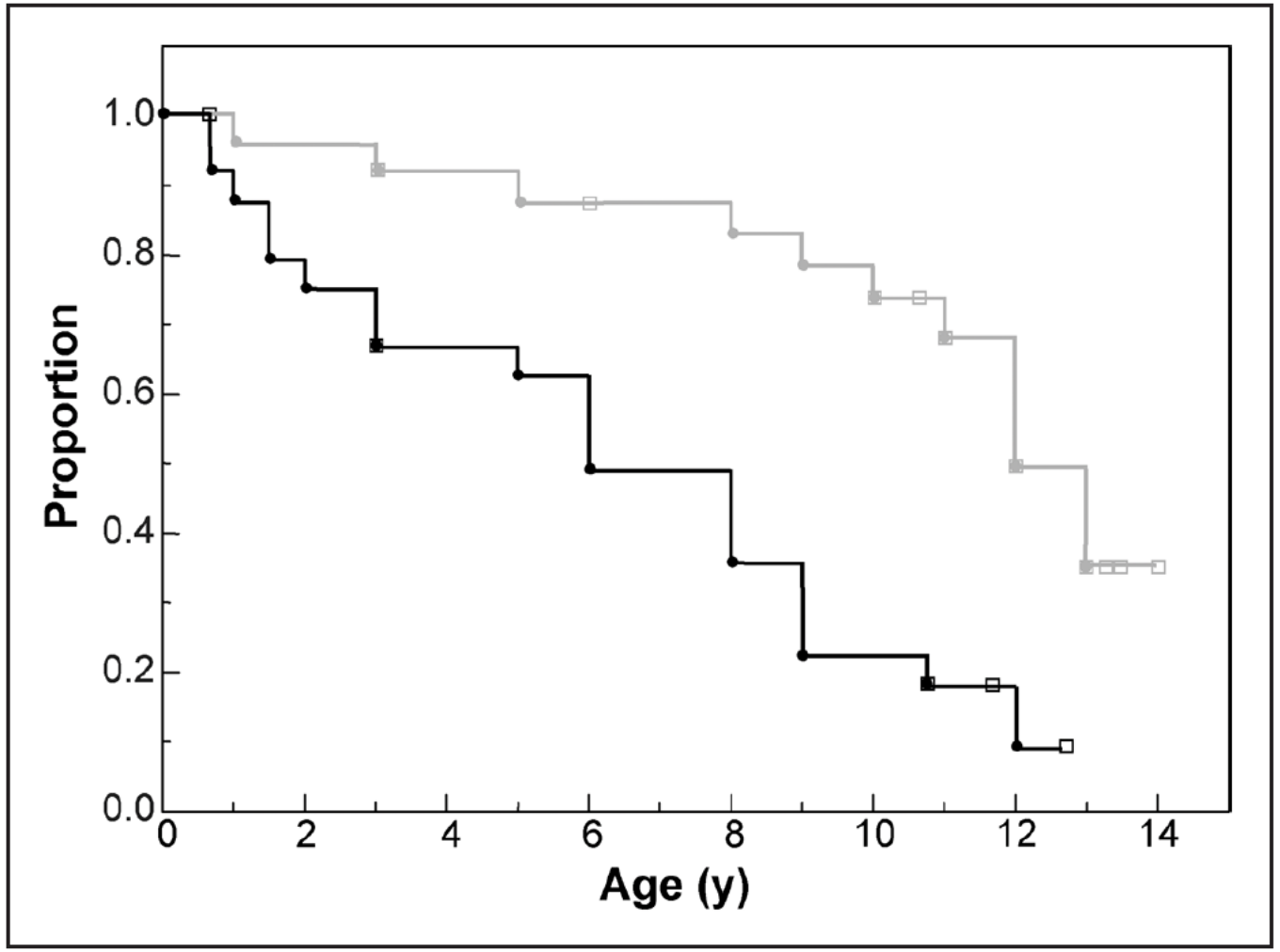


Figure 1—Results of Kaplan-Meier analysis for proportion of Labrador Retrievers (gray line = restricted-fed dogs [n = 24]; black line = control-fed dogs [24]) without radiographic evidence of hip joint osteoarthritis.

Smith GK, Paster ER, Powers MY, Lawler DF, Biery DN, Shofer FS, McKelvie PJ, Kealy RD. Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. J Am Vet Med Assoc. 2006 Sep 1;229(5):690-3

Caloric Restriction

- Dogs
  - Lifespan (median and maximum)
  - Age-associated disease
  - Metabolic health (glucose, insulin)

Insulin sensitivity paired analysis in 9- to 12-y-old control- and restricted-fed dogs

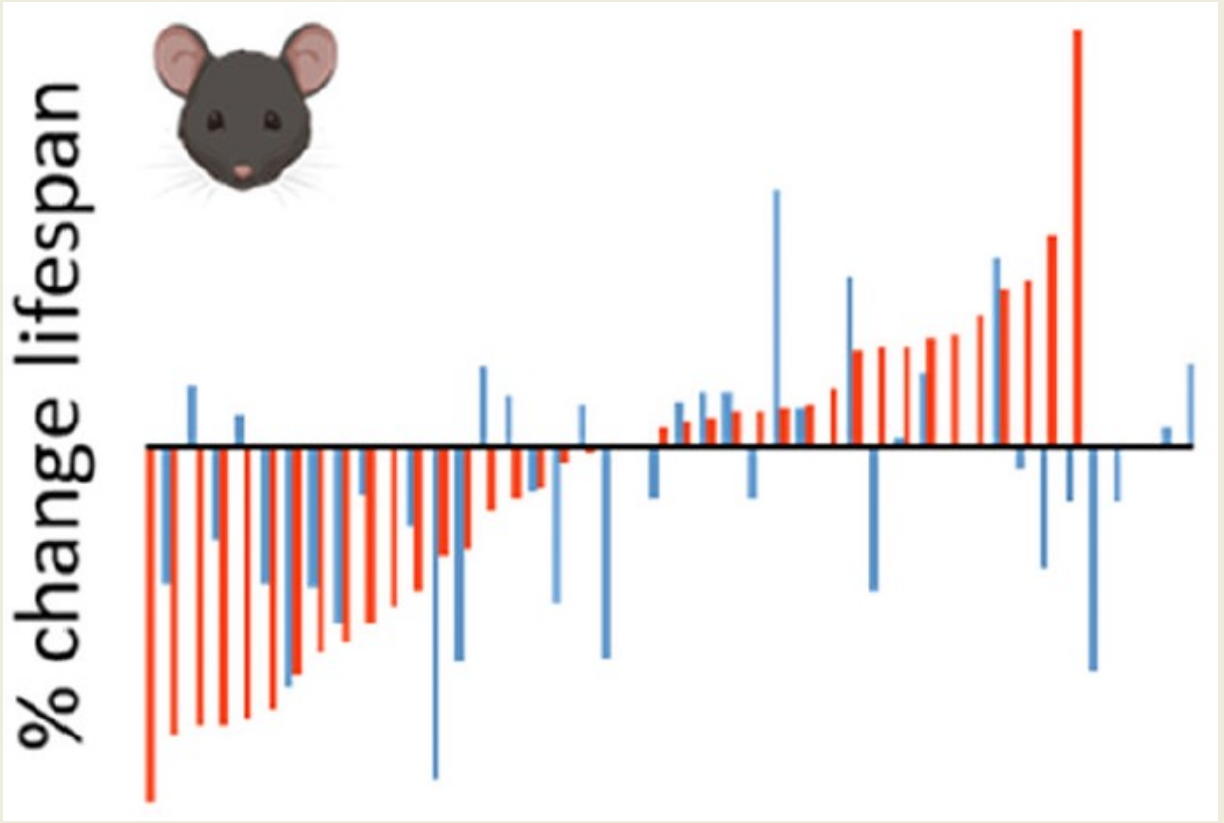
Age, *y*	Pairs, *n*	Treatment	Sensitivity[1,2]
			min^{-1}/(*pmol insulin*$^{-1}$ · *min*)
9	20	Restricted	0.527 ± 0.059
		Control	0.223 ± 0.043
		Difference	0.302 ± 0.078*
10	13	Restricted	0.553 ± 0.077
		Control	0.210 ± 0.025
		Difference	0.344 ± 0.081*
11	9	Restricted	0.505 ± 0.094
		Control	0.187 ± 0.014
		Difference	0.318 ± 0.102*
12	6	Restricted	0.277 ± 0.057
		Control	0.159 ± 0.032
		Difference	0.118 ± 0.067

[1] Values are means ± SEM.
[2] * Different from control-fed dogs, $P < 0.05$.

Larson, B. T., Lawler, D.F., Spitznagel, E. L., & Kealy, R.D.. Improved glucose tolerance with lifetime diet restriction favorably affects disease and survival in dogs. J Nutr. 2003;133(9), 2887-2892.

Caloric Restriction

- Caveats
  - Doesn’t always work
  - Can be detrimental
  - Confounders
    - Age started
    - Diet composition
    - Comparison group
  - Not practical
- Lessons
  - Less is more
  - Identify mechanisms



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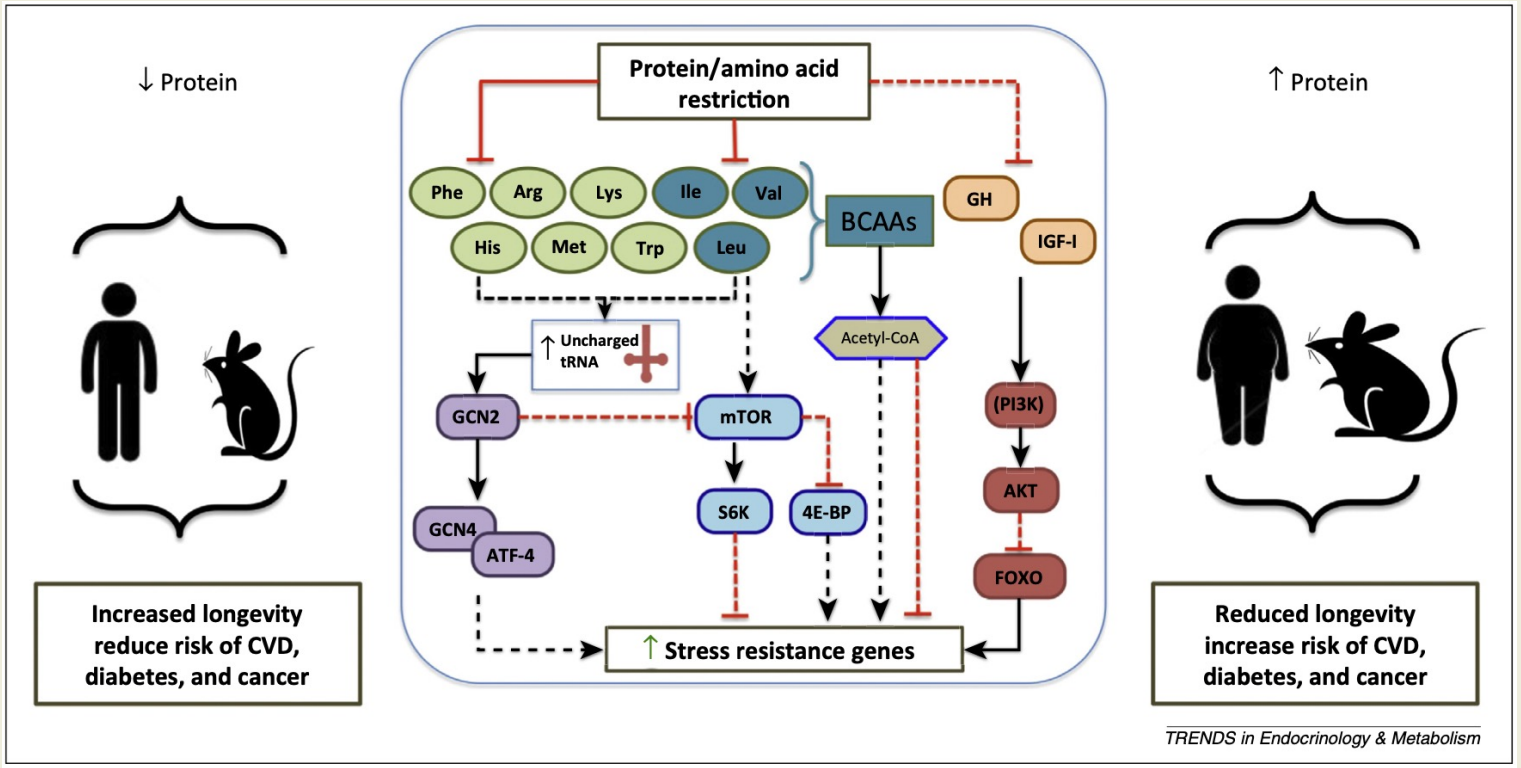
Protein Restriction

- Extends lifespan & healthspan
  - Flies, worms, mice, rats



Mirzaei H, Suarez JA, Longo VD. Protein and amino acid restriction, aging and disease: from yeast to humans. Trends Endocrinol Metab. 2014;25(11):558-66.

Protein Restriction

- Extends lifespan & healthspan
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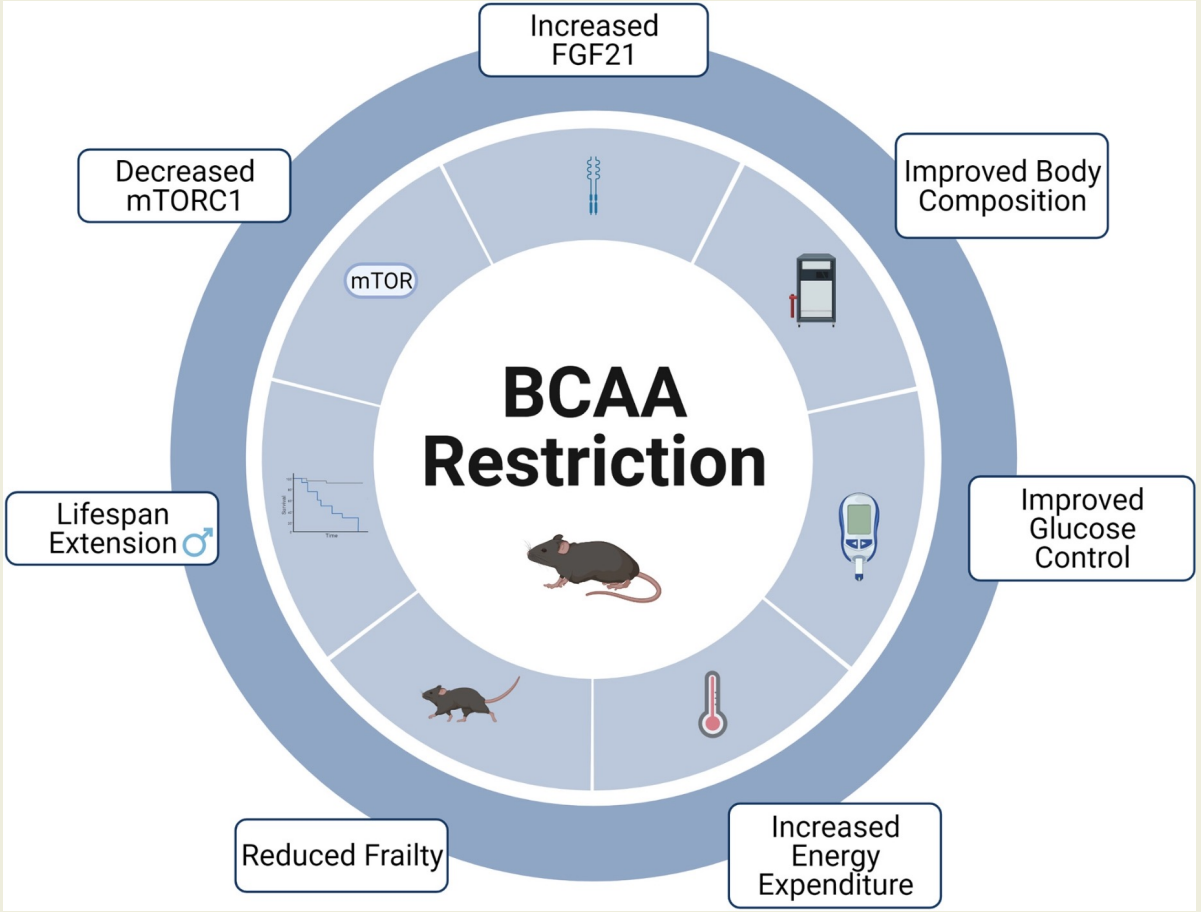
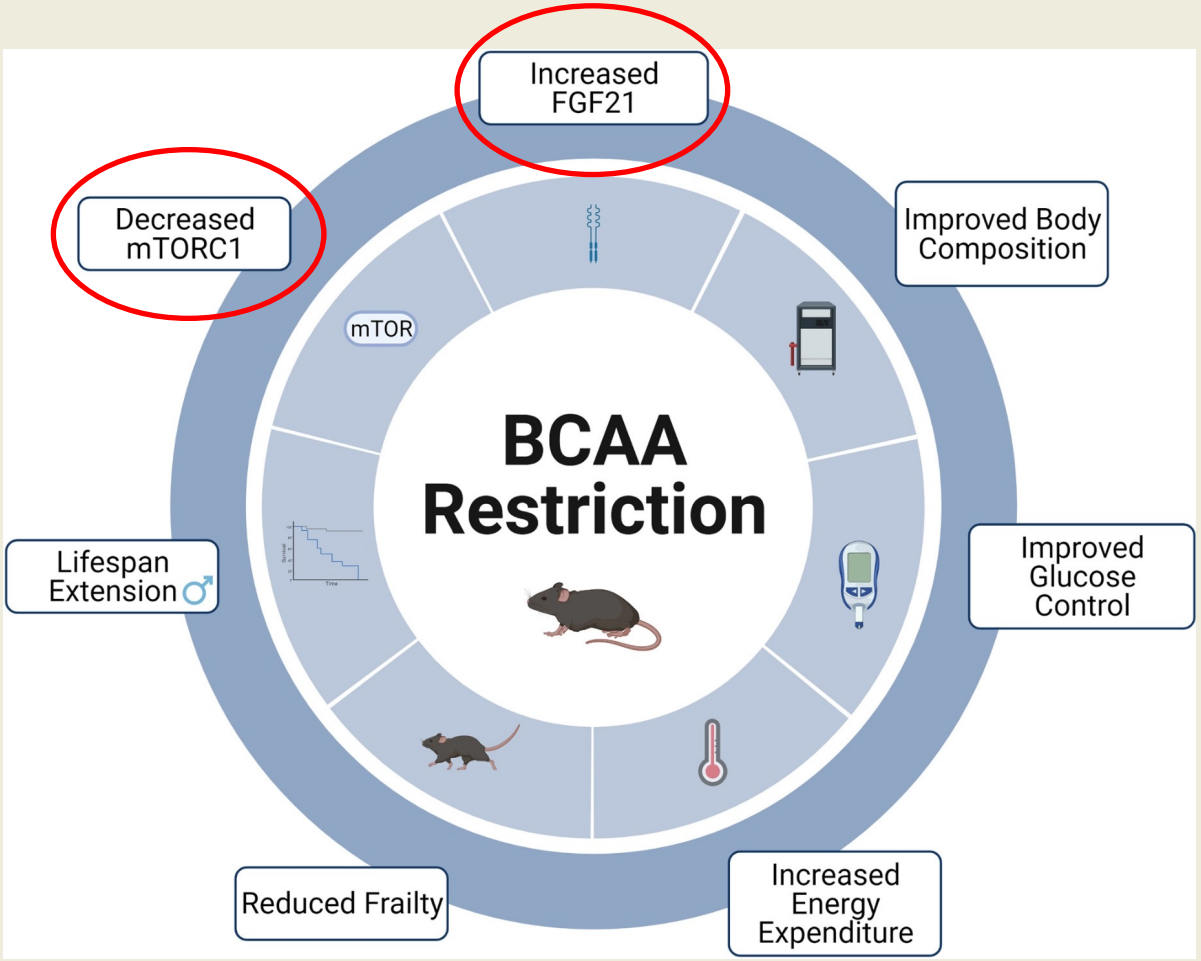
- Specific Amino Acids
  - Methionine/cysteine
  - BCAA



Trautman ME, Richardson NE, Lamming DW. Protein restriction and branched-chain amino acid restriction promote geroprotective shifts in metabolism. Aging Cell. 2022;21(6):e13626.

Protein Restriction

- Extends lifespan & healthspan
  - Flies, worms, mice, rats
- Specific Amino Acids
  - Methionine/cysteine
  - BCAA
- Mechanisms
  - mTORC1 inhibition (e.g. isoleucine)
  - FGF21 activation



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Protein Restriction

- Caveats
  - Diets often also CR

Protein Restriction

- **Caveats**
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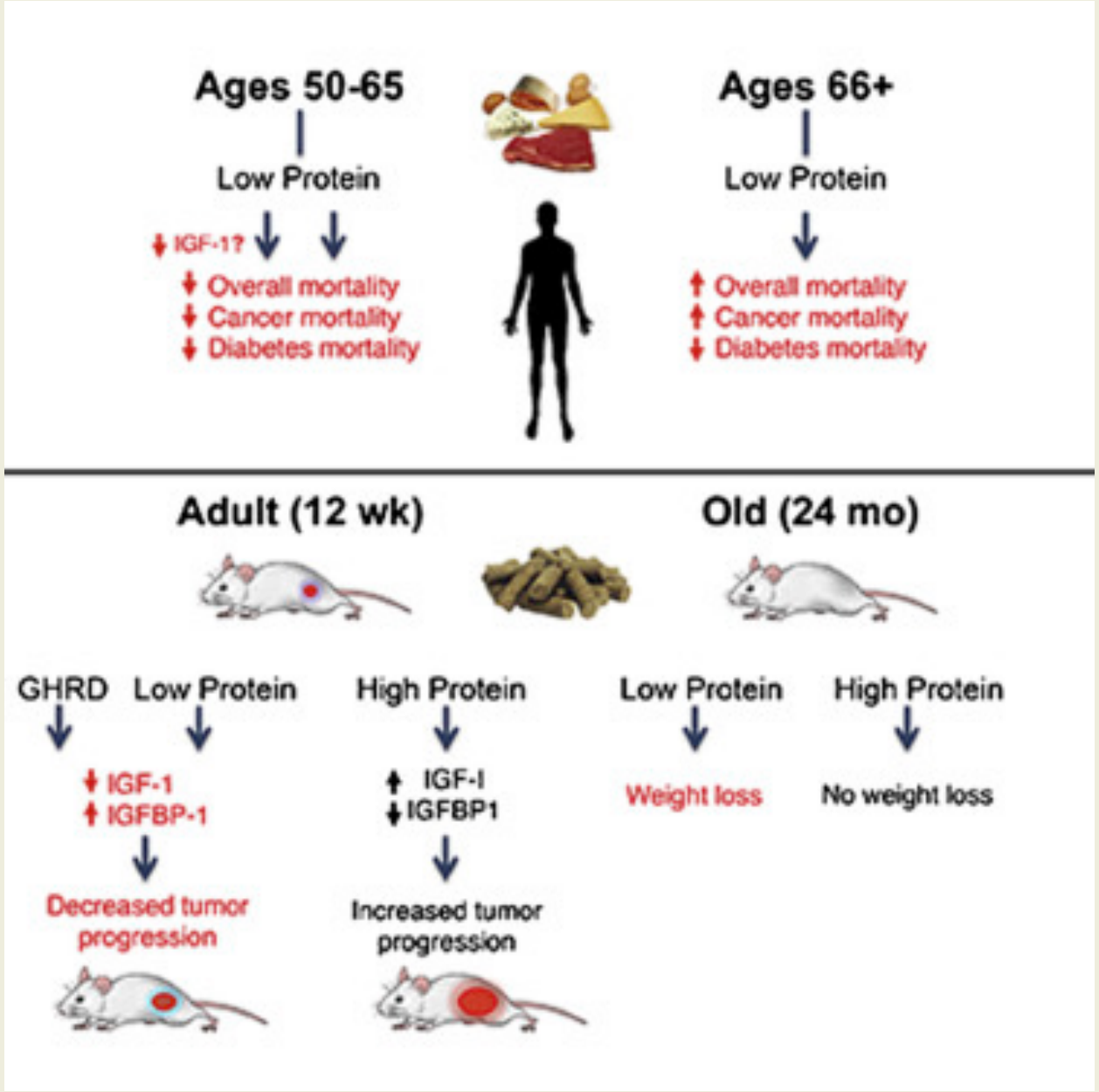
  - Isocaloric PR << CR

Protein Restriction

- Caveats
  - Diets often also CR
  - Isocaloric PR << CR
  - Effects age-dependent



Levine ME, Suarez JA, Brandhorst S, et a.. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab. 2014;19(3):407-17.

Protein Restriction

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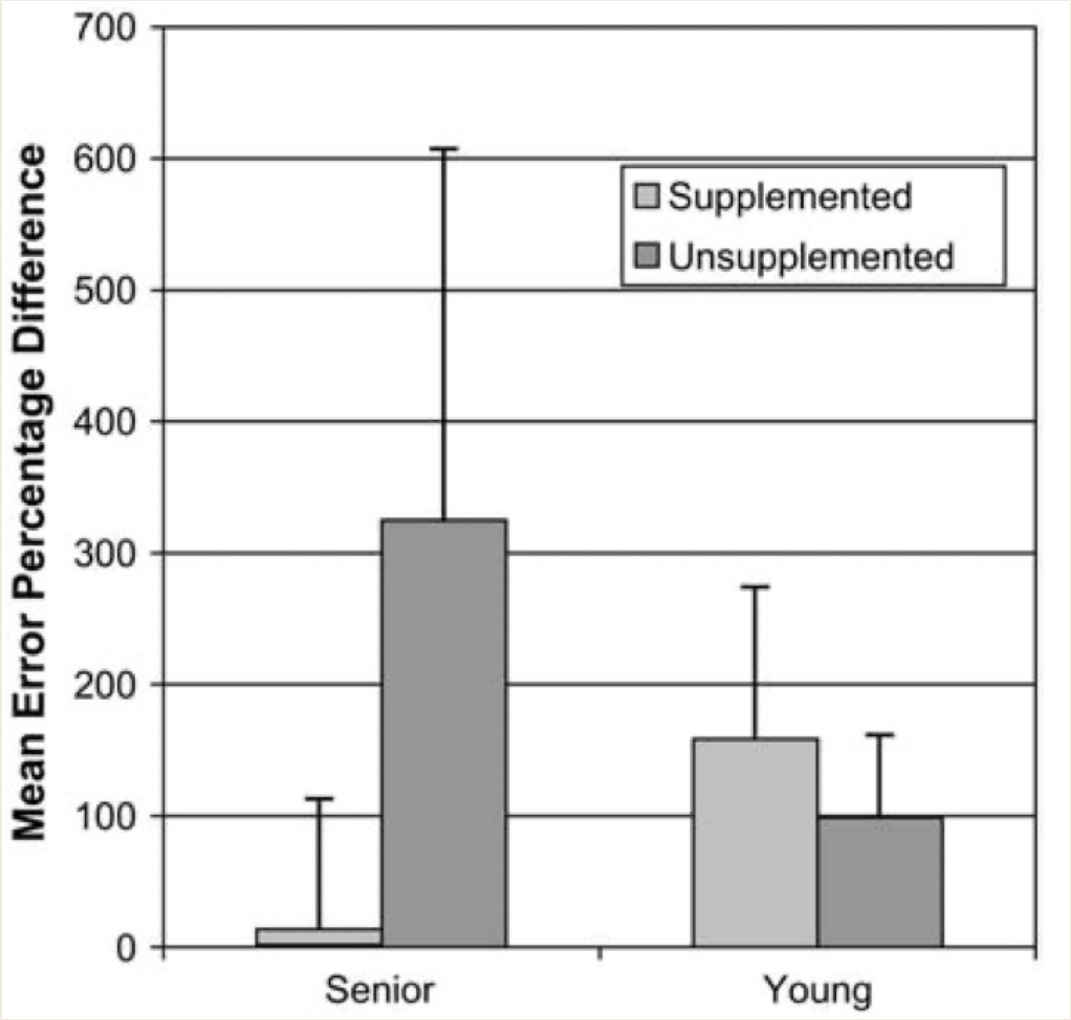

Fretwell LK, McCune S, Fone JV, Yates DJ. The effect of supplementation with branched-chain amino acids on cognitive function in active dogs. J Nutr. 2006;136(7 Suppl):2069S-2071S.

Protein Restriction

- Caveats
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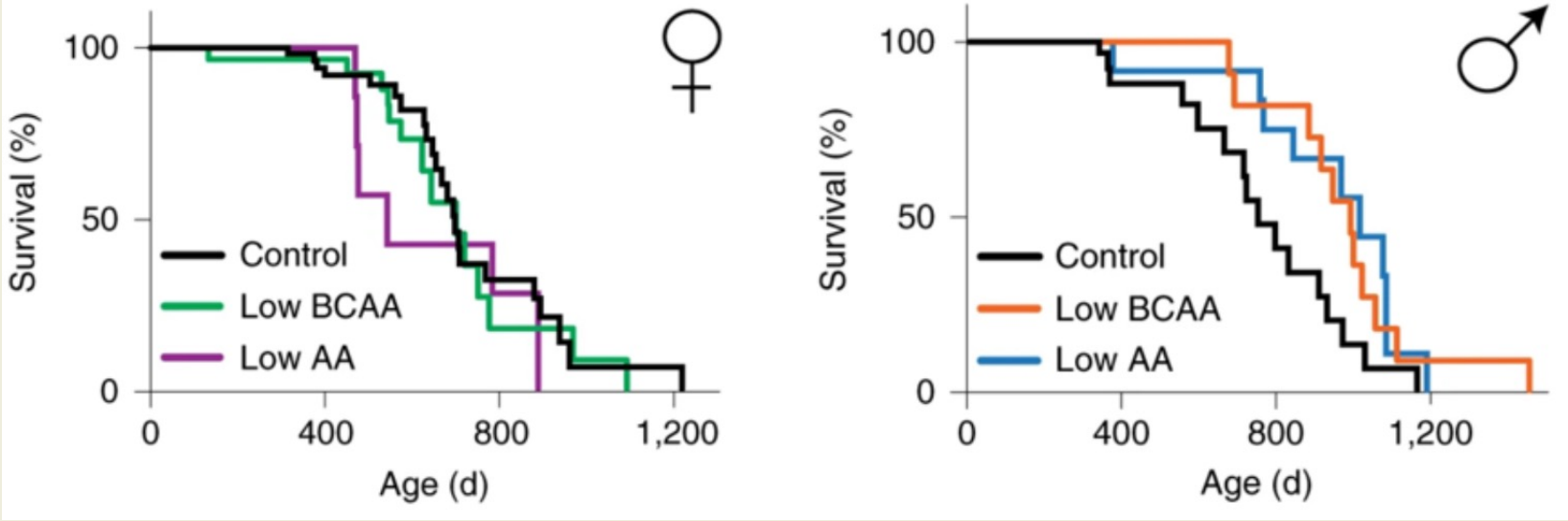
  - Effects age-dependent
  - Sometimes sex-specific



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Protein Restriction

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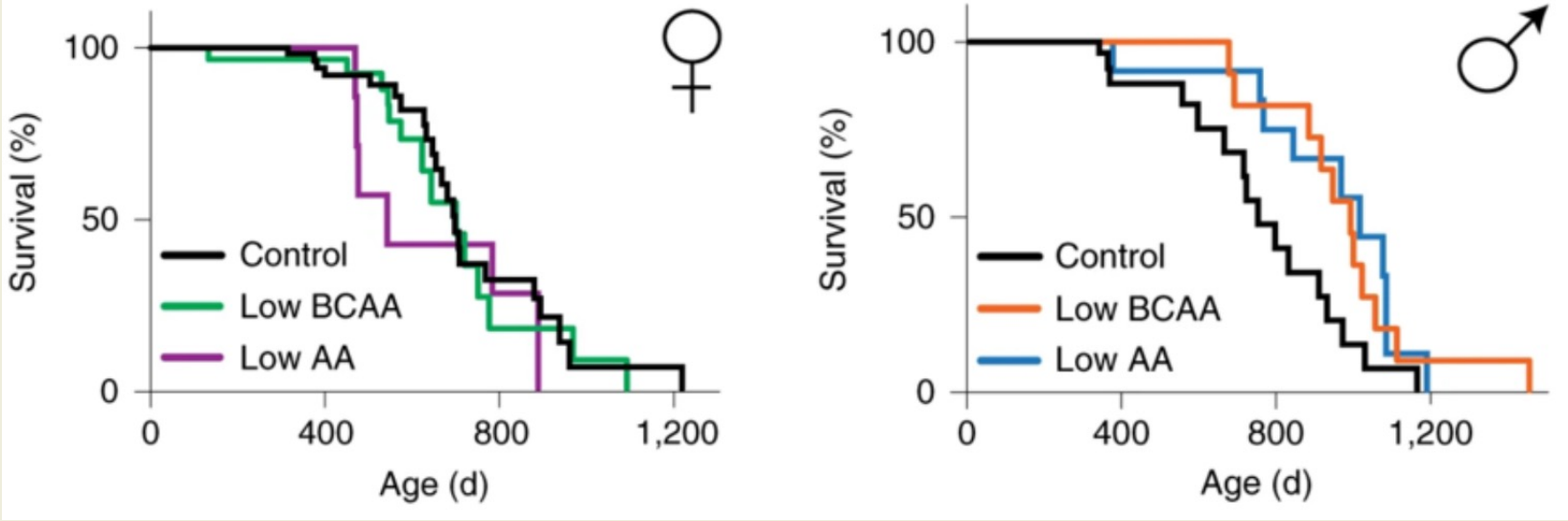

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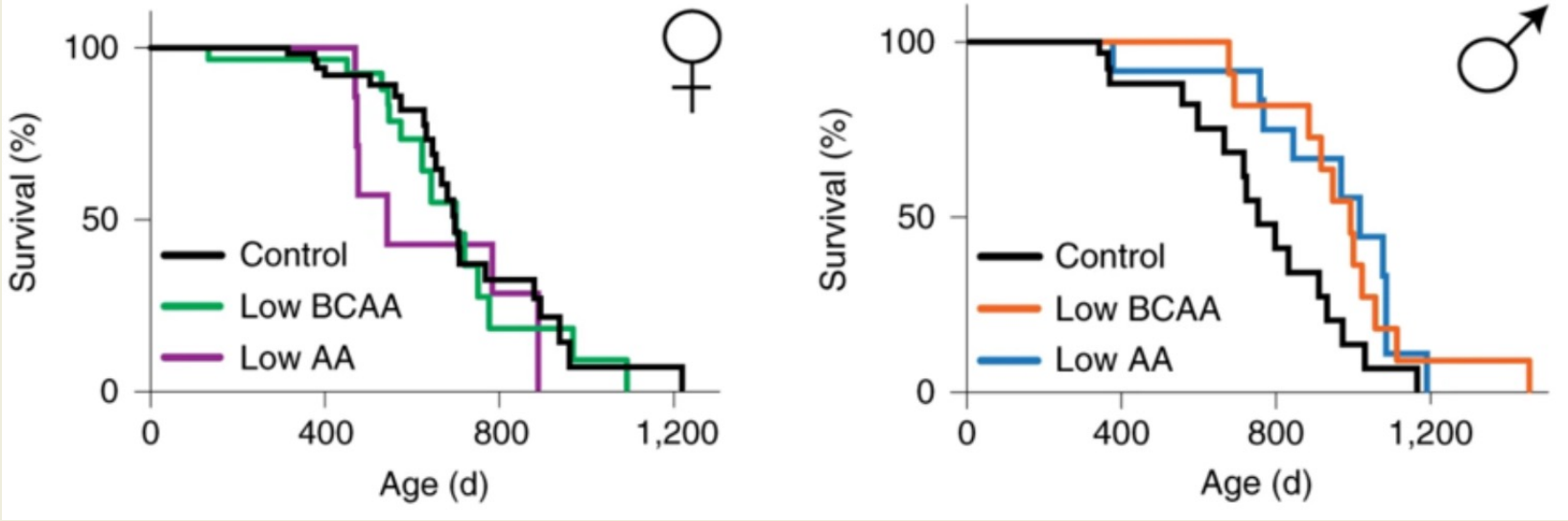
Protein Restriction

- **Caveats**
  - Diets often also CR
  - Isocaloric PR << CR
  - Effects age-dependent
  - Sometimes sex-specific
  - Cats ≠ Dogs ≠ Rats
- **Lessons**
  - Can choose specific targets
  - No one-size-fits-all



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→ Targeting Mechanisms of Aging

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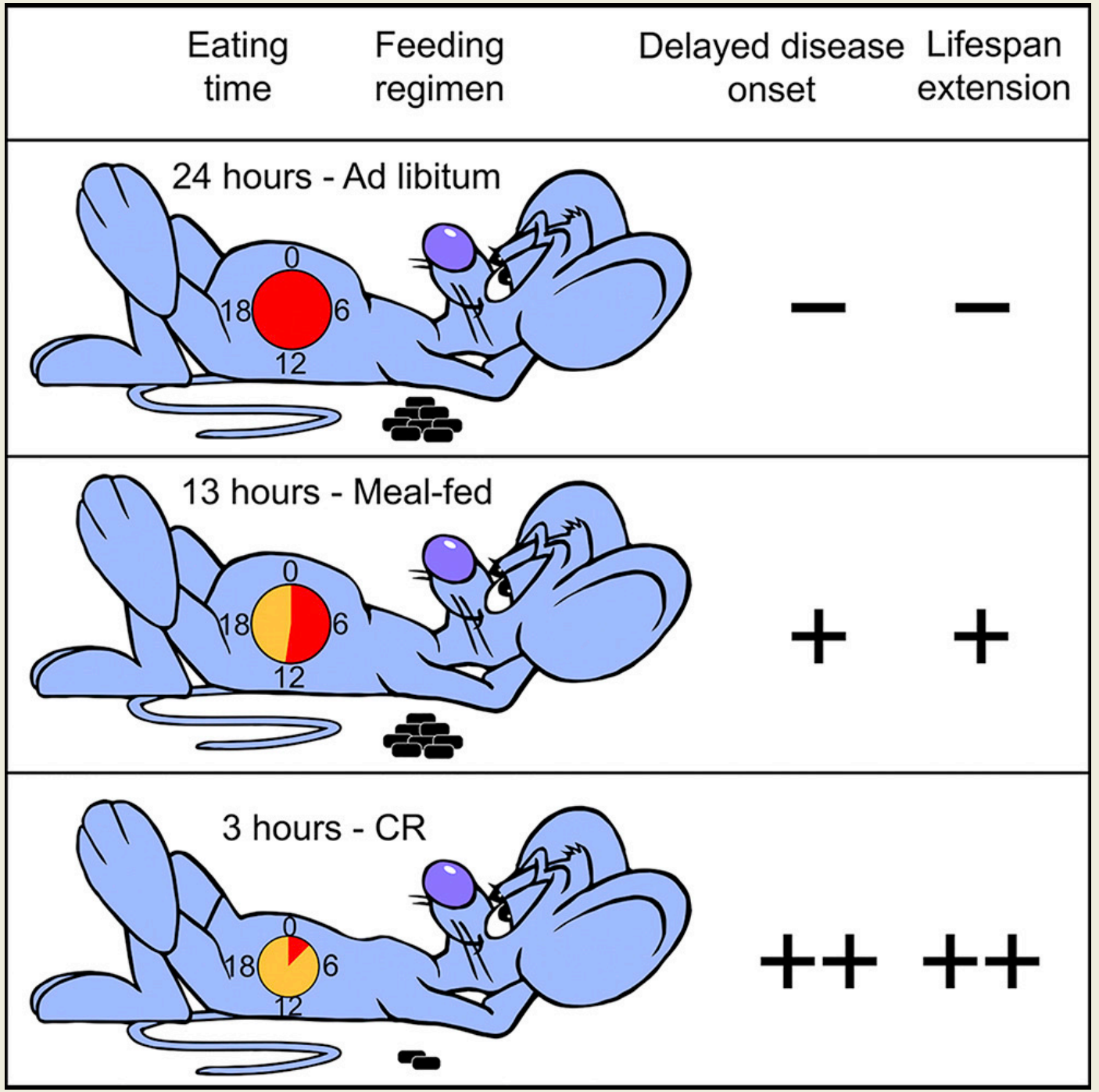
Fasting

- Increases lifespan & healthspan



Mitchell SJ, Bernier M, Mattison JA, et al. Fasting Improves Health and Survival in Male Mice Independent of Diet Composition and Calories. Cell Metab. 2019;29(1):221-228.e3

Fasting

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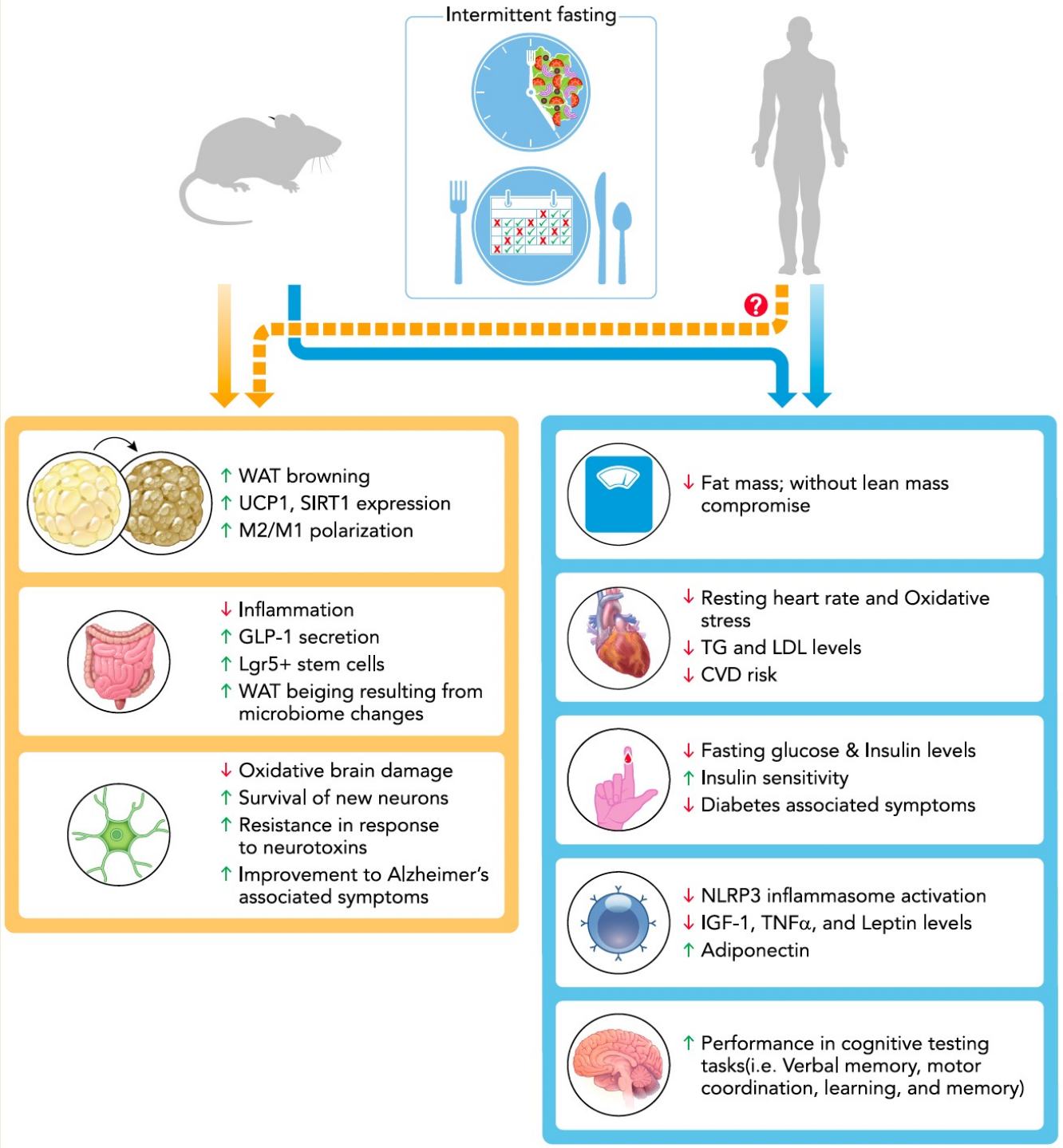
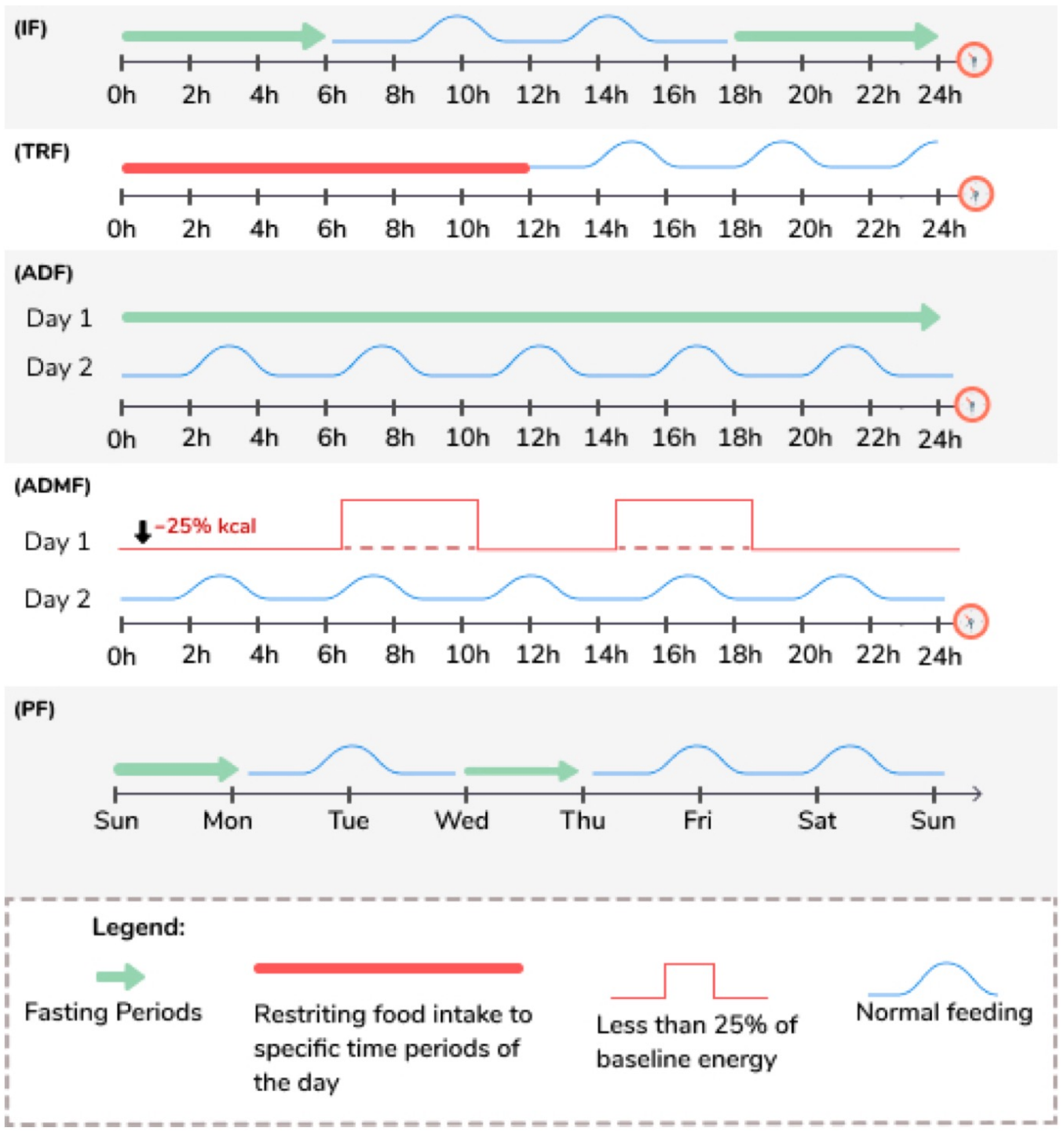
- Improves metabolic health



Lee JH, Verma N, Thakkar N, Yeung C, Sung HK. Intermittent Fasting: Physiological Implications on Outcomes in Mice and Men. Physiology (Bethesda). 2020 May 1;35(3):185-195

Fasting

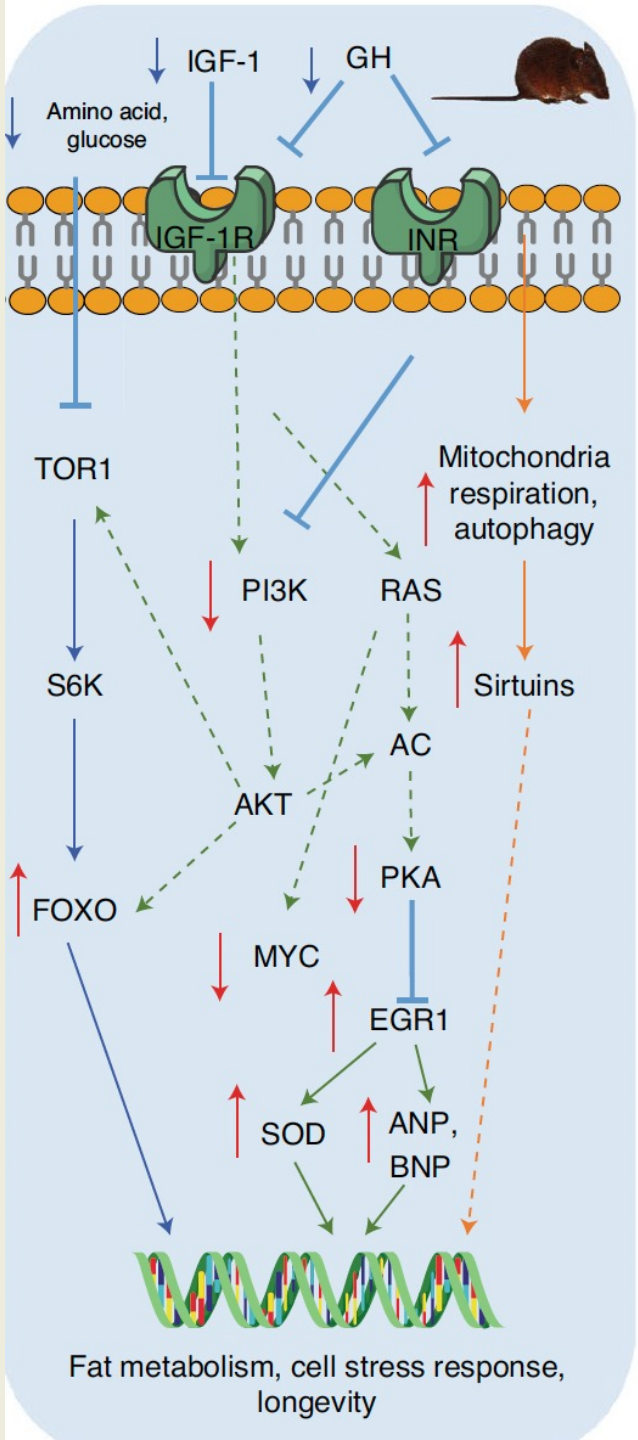
- Increases lifespan & healthspan
- Improves metabolic health
- Various Protocols
  - Fasting/Feeding in various ratios
  - Time-restricted feeding (TRF)
  - Fasting-mimicking diets (FMD)



Napoleão A, Fernandes L, Miranda C, Marum AP. Effects of Calorie Restriction on Health Span and Insulin Resistance: Classic Calorie Restriction Diet vs. Ketosis-Inducing Diet. Nutrients. 2021;13(4):1302.

Fasting

- Mechanisms
  - Induces ketosis
  - ↓IGF-1/insulin
  - ↓ mTORC1
  - ↑ FOXO, ↑ FGF21



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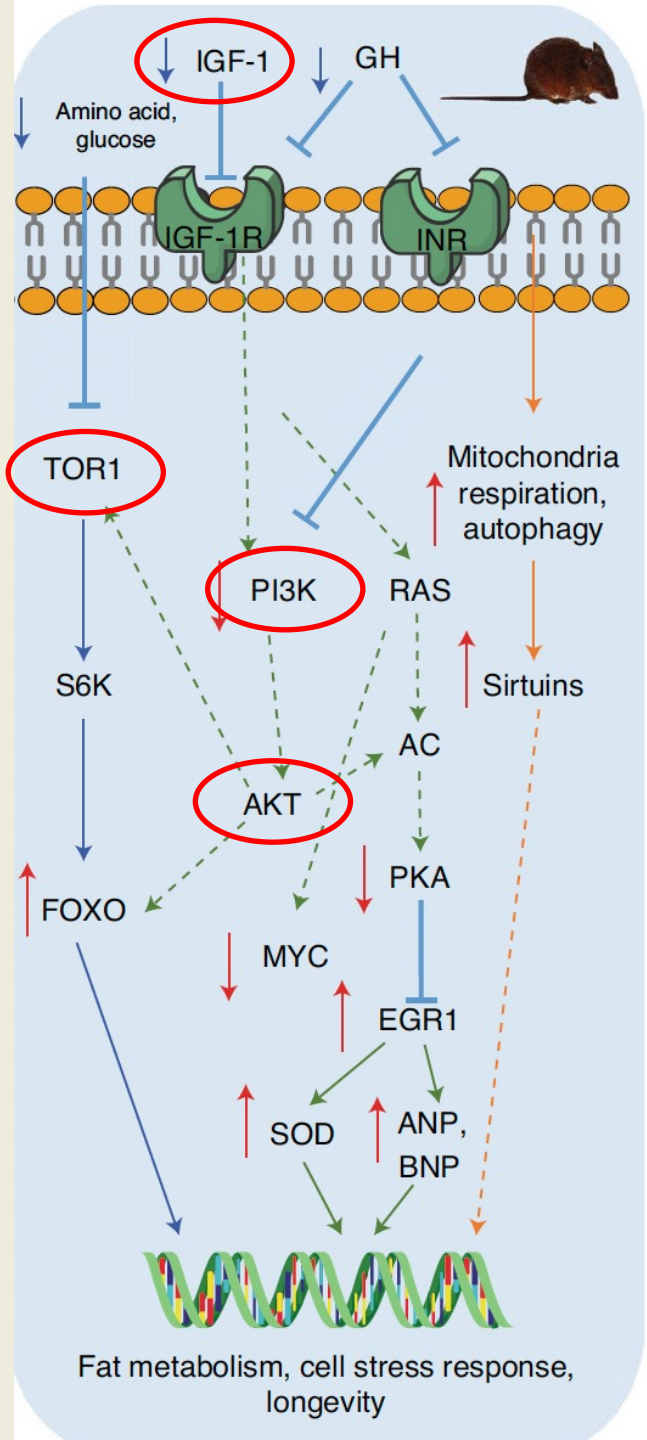

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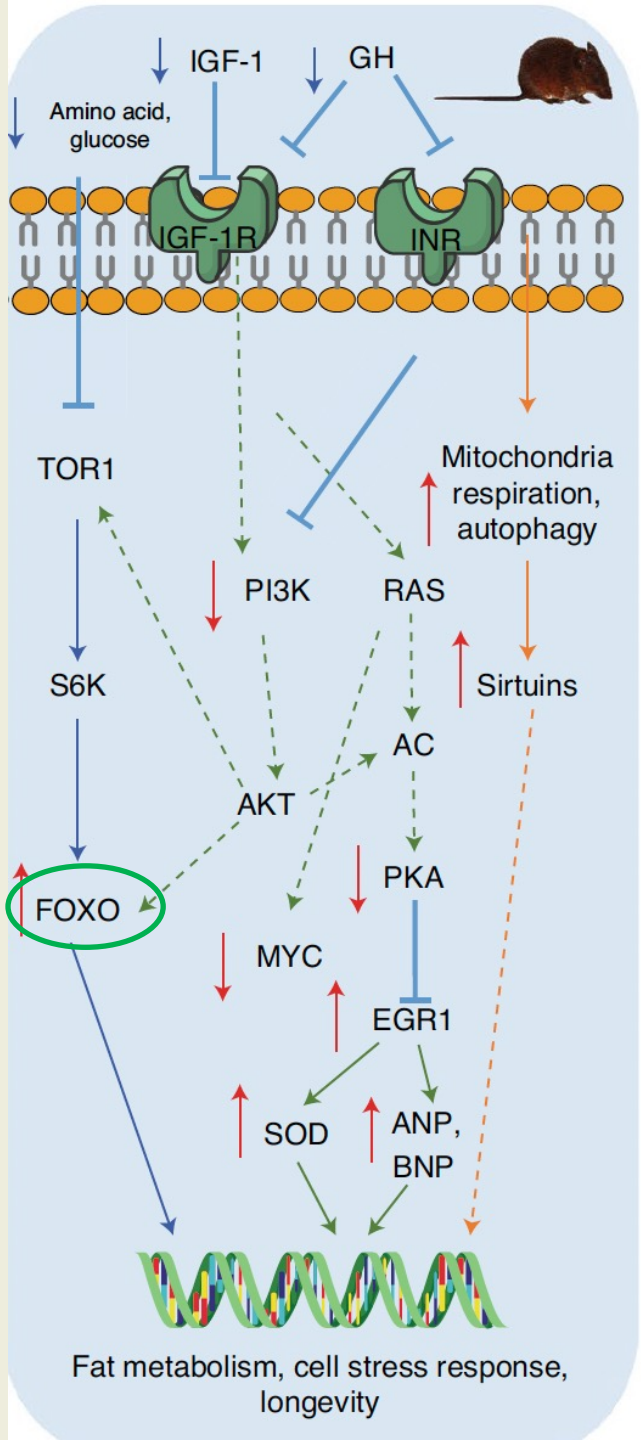

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Fasting

- Caveats
  - Just CR? < CR?

Fasting

- Caveats
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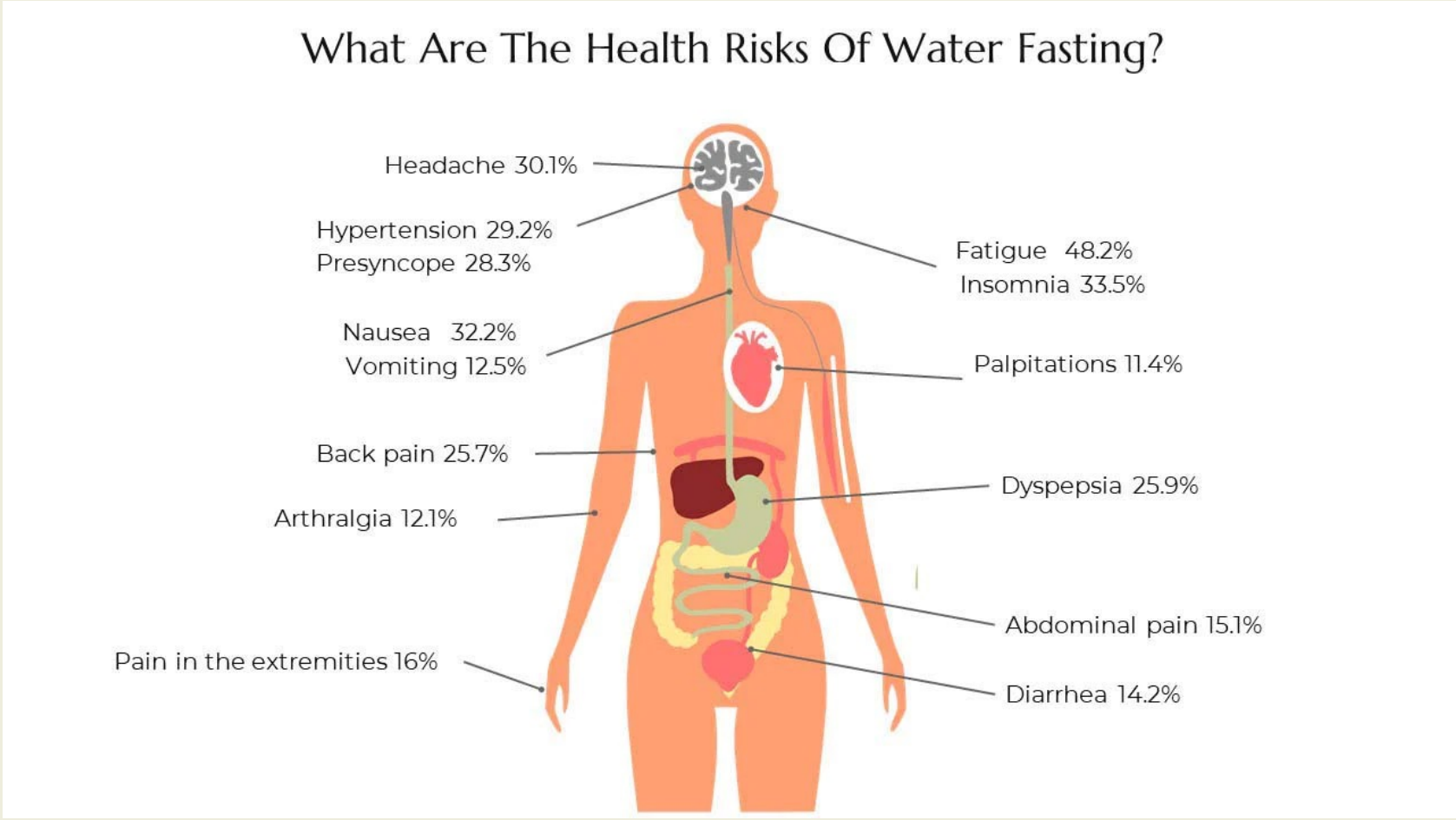
  - Adverse effects
    - Hypoglycemia
    - Hypotension
    - Loss of LBM
    - Disordered eating



Finnell JS, Saul BC, Goldhamer AC, Myers TR. Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. BMC Complement Altern Med. 2018;18(1):67.

Fasting

- Caveats
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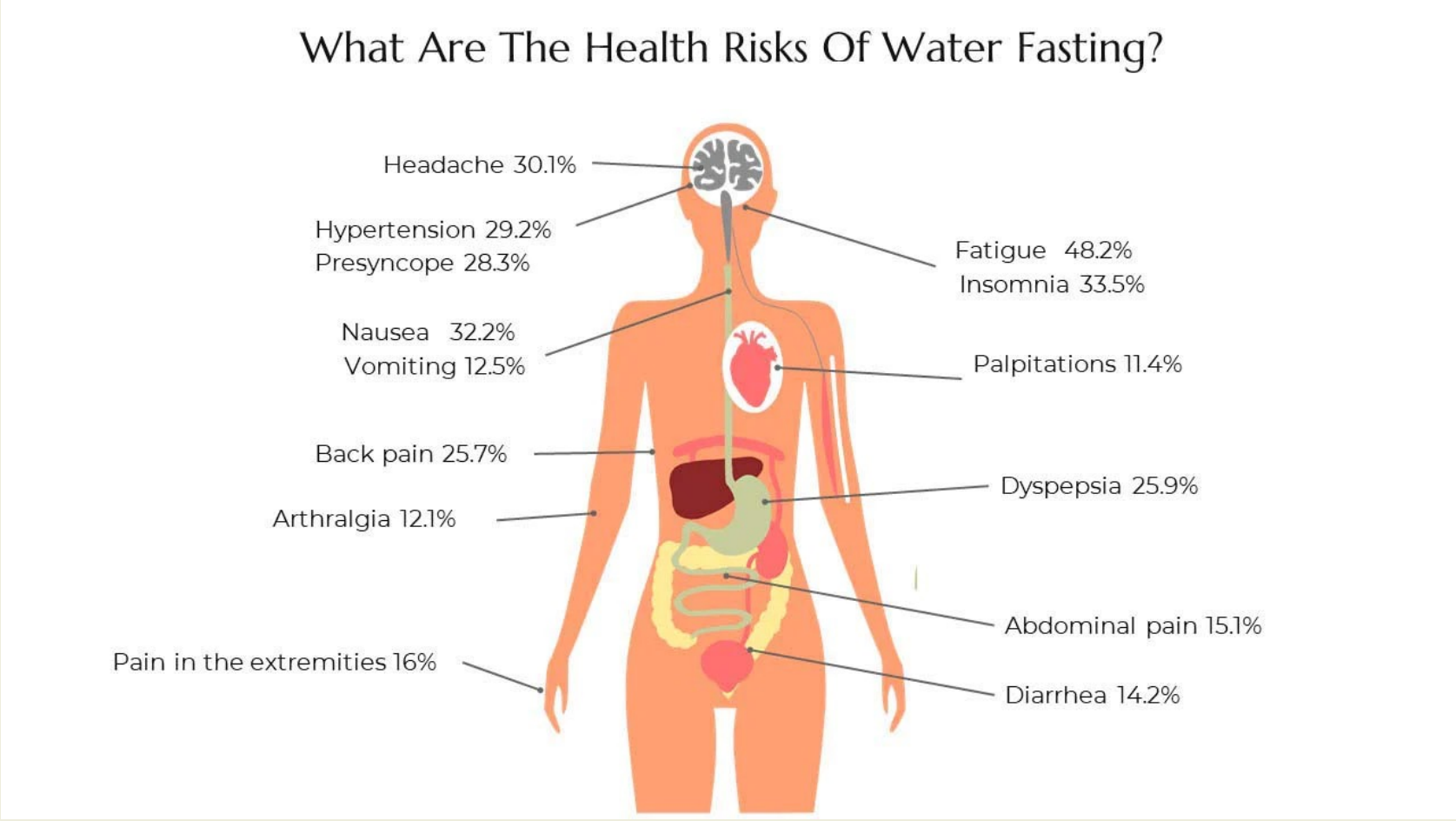
    - Hypotension
    - Loss of LBM
    - Disordered eating
  - Cats ≠ Dogs ≠ Rats



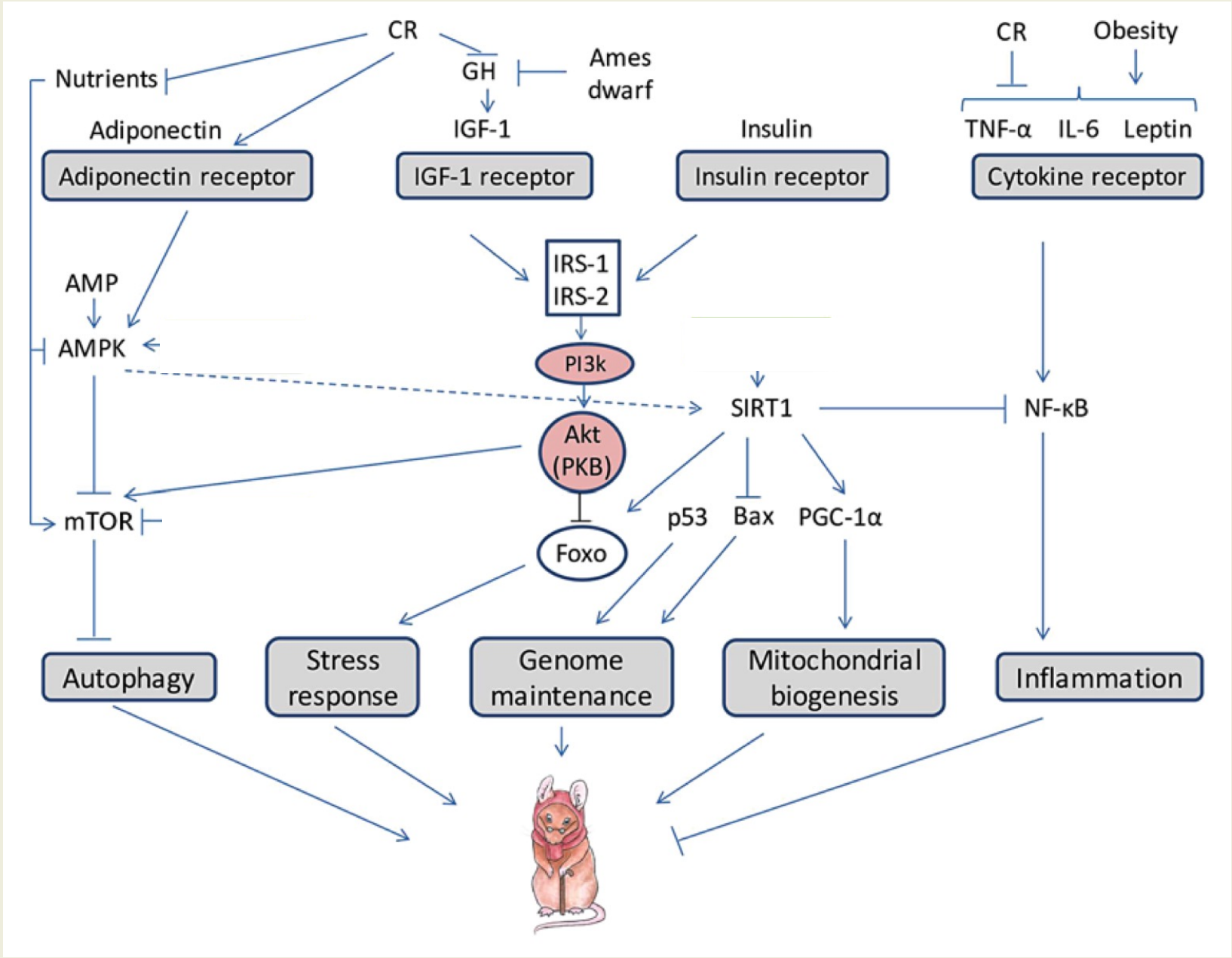
Finnell JS, Saul BC, Goldhamer AC, Myers TR. Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. BMC Complement Altern Med. 2018;18(1):67.

→ Targeting Mechanisms of Aging

- Caloric Restriction
- Protein/Amino Acid Restriction
- Fasting/Fasting Mimicking Diets
- Pharmaceuticals

Pharmaceuticals

- Principles
  - Target specific pathways
  - Consistent/predictable effects
  - Clinically practical



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Pharmaceuticals

- Principles
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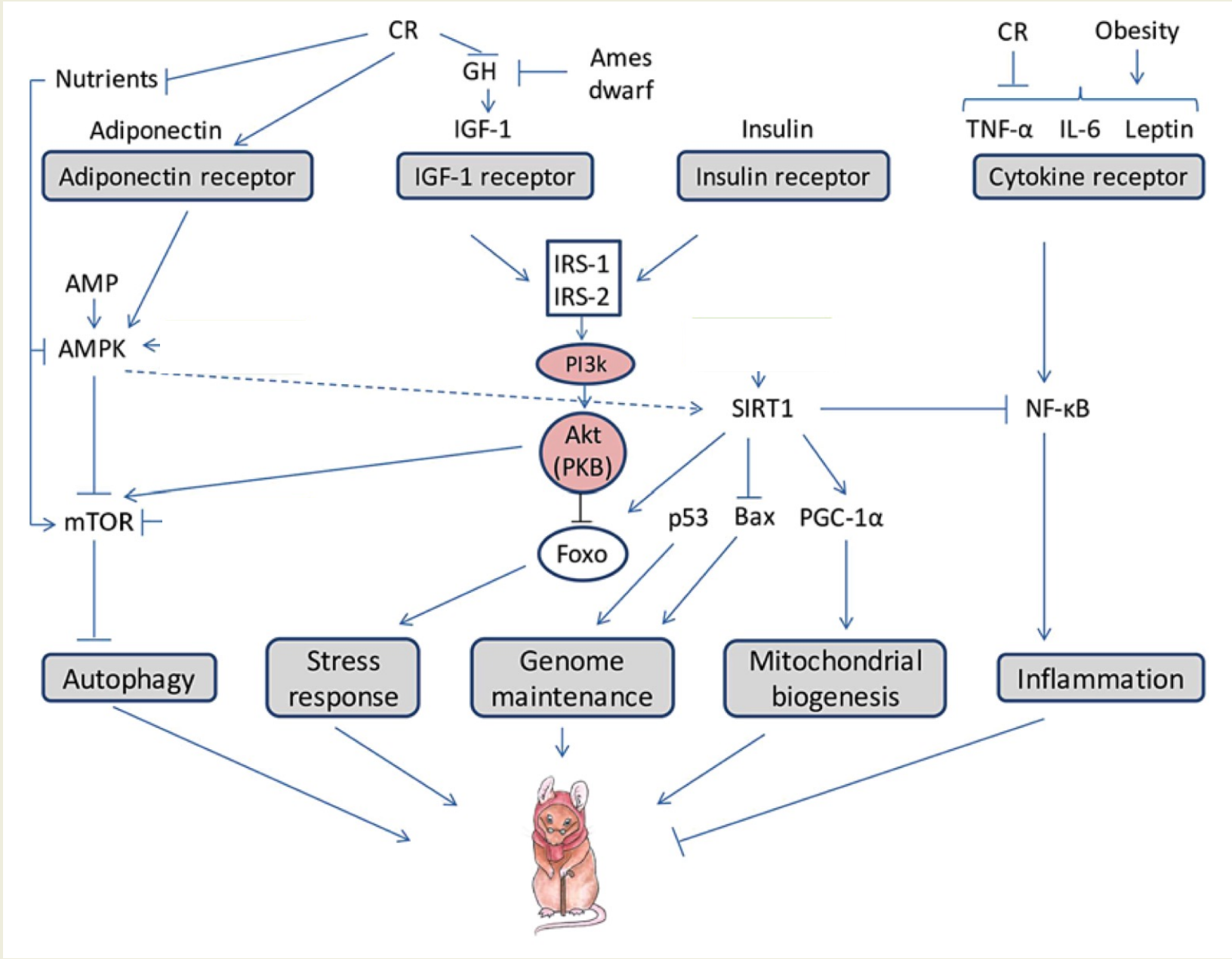
- CR Mimetics



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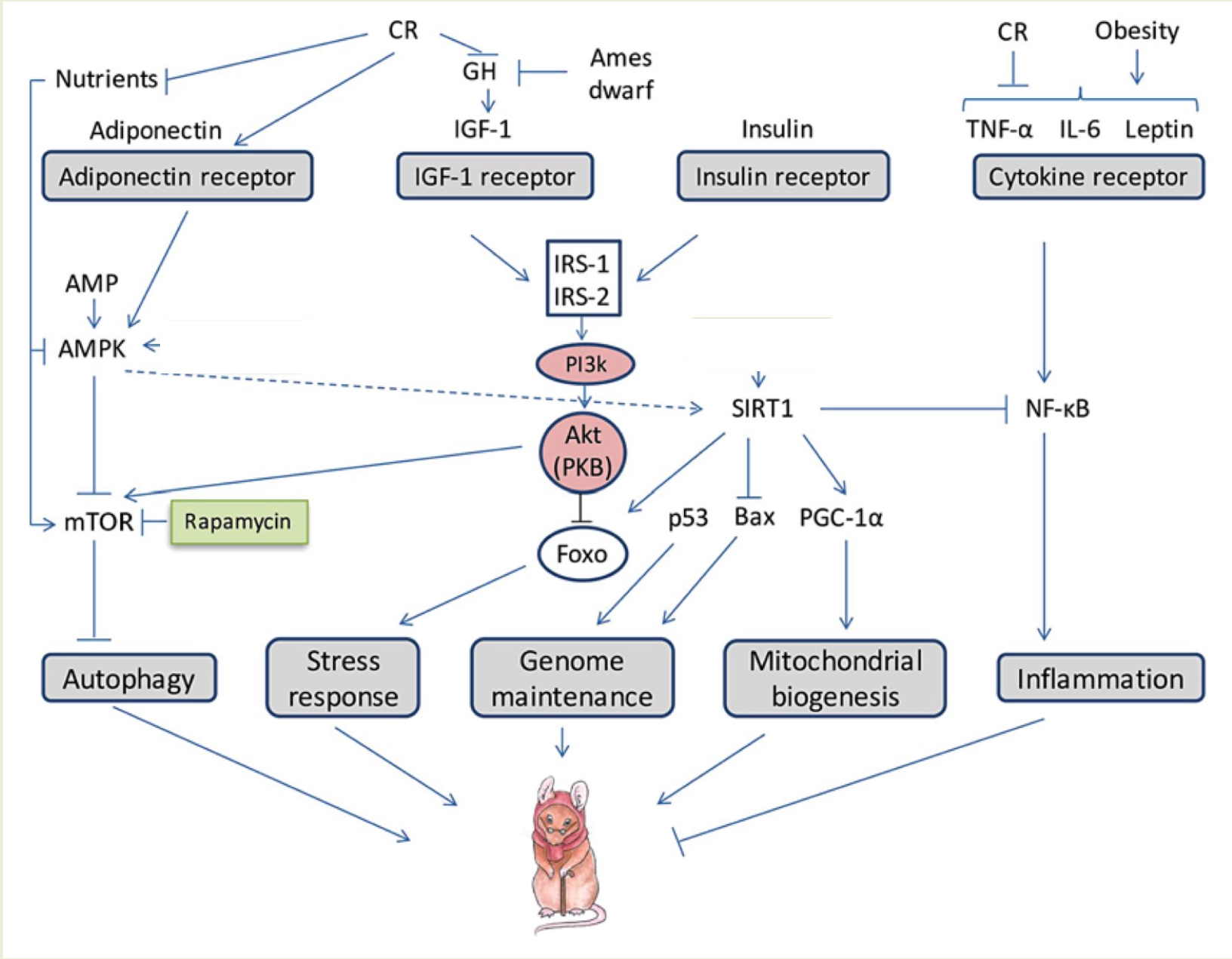
Pharmaceuticals

- Principles
  - Target specific pathways
  - Consistent/predictable effects
  - Clinically practical
- CR Mimetics
  - Rapamycin



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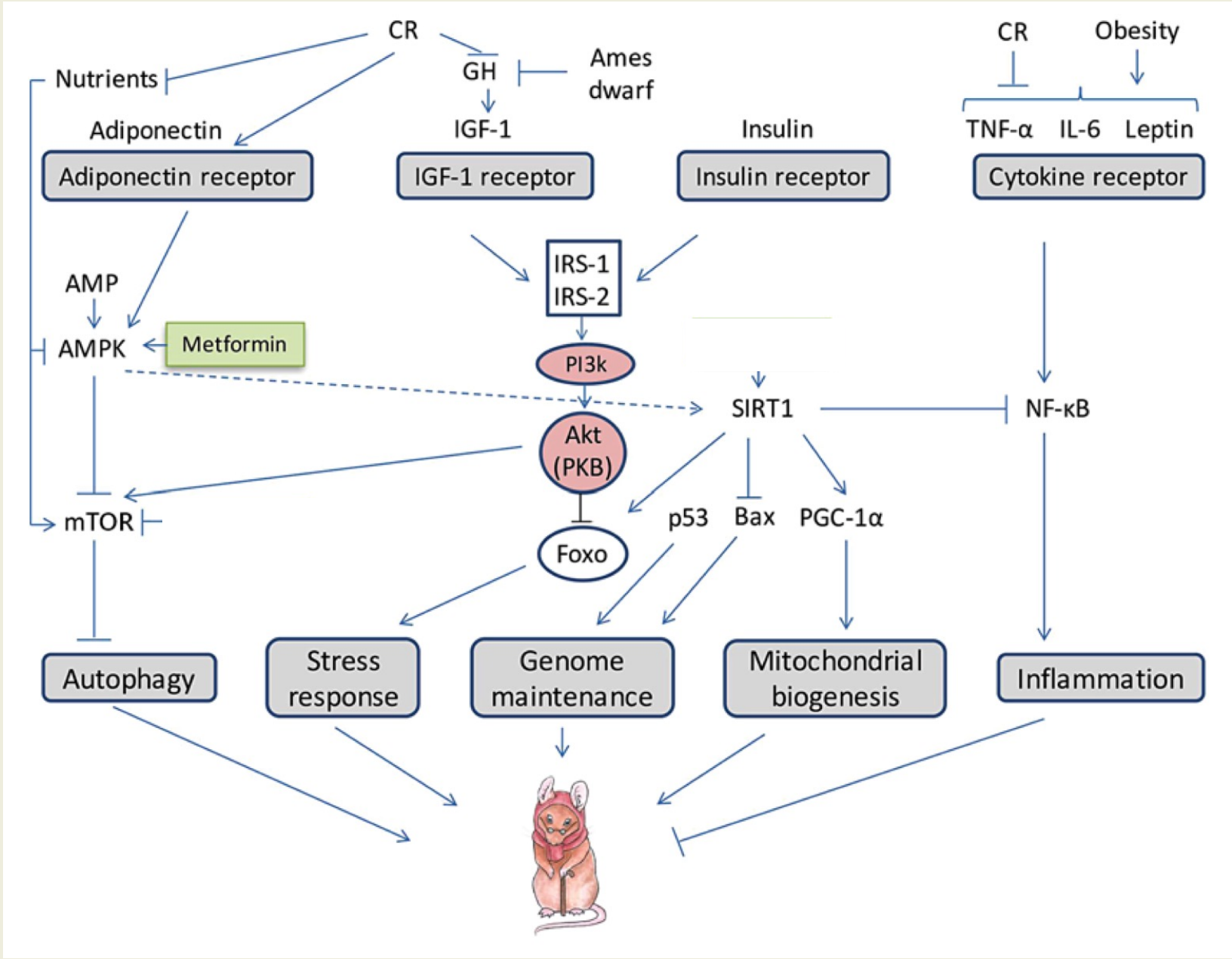
Pharmaceuticals

- Principles
  - Target specific pathways
  - Consistent/predictable effects
  - Clinically practical
- CR Mimetics
  - Rapamycin
  - Metformin



Azzu V, Valencak TG. Energy Metabolism and Ageing in the Mouse: A Mini-Review. Gerontology. 2017;63(4):327-336.

Clinical Implications

→ Nutrition can Impact Aging

- Extend lifespan
- Extend healthspan
- Alter aging mechanisms

Main Principles

- Less is more
- Biology is complicated
  - patient factors
  - dietary factors
  - non-dietary factors

Main Principles

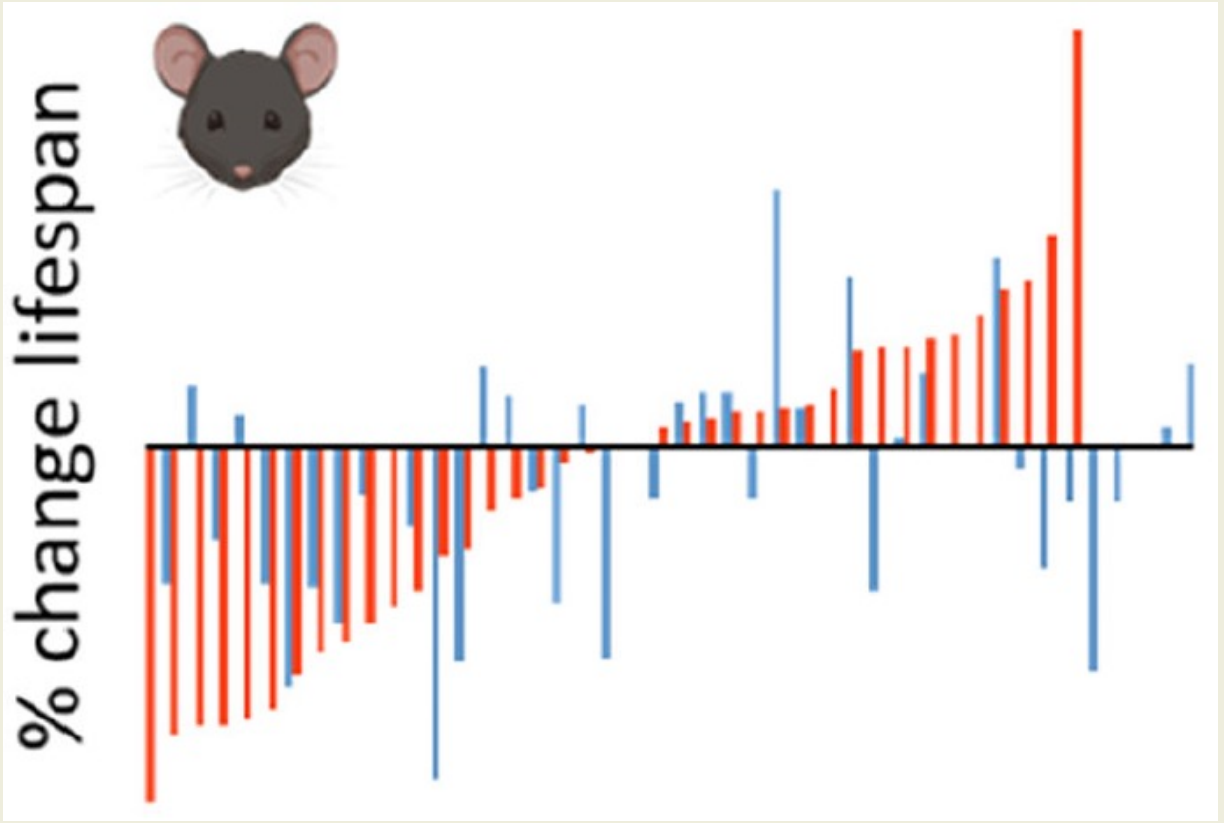
- Less is more
- Biology is complicated
  - patient factors
  - dietary factors
  - non-dietary factors

- Lifestyle 🚫 Drugs


WELCOME TO
REALITY

Fictions of Anti-aging Diets

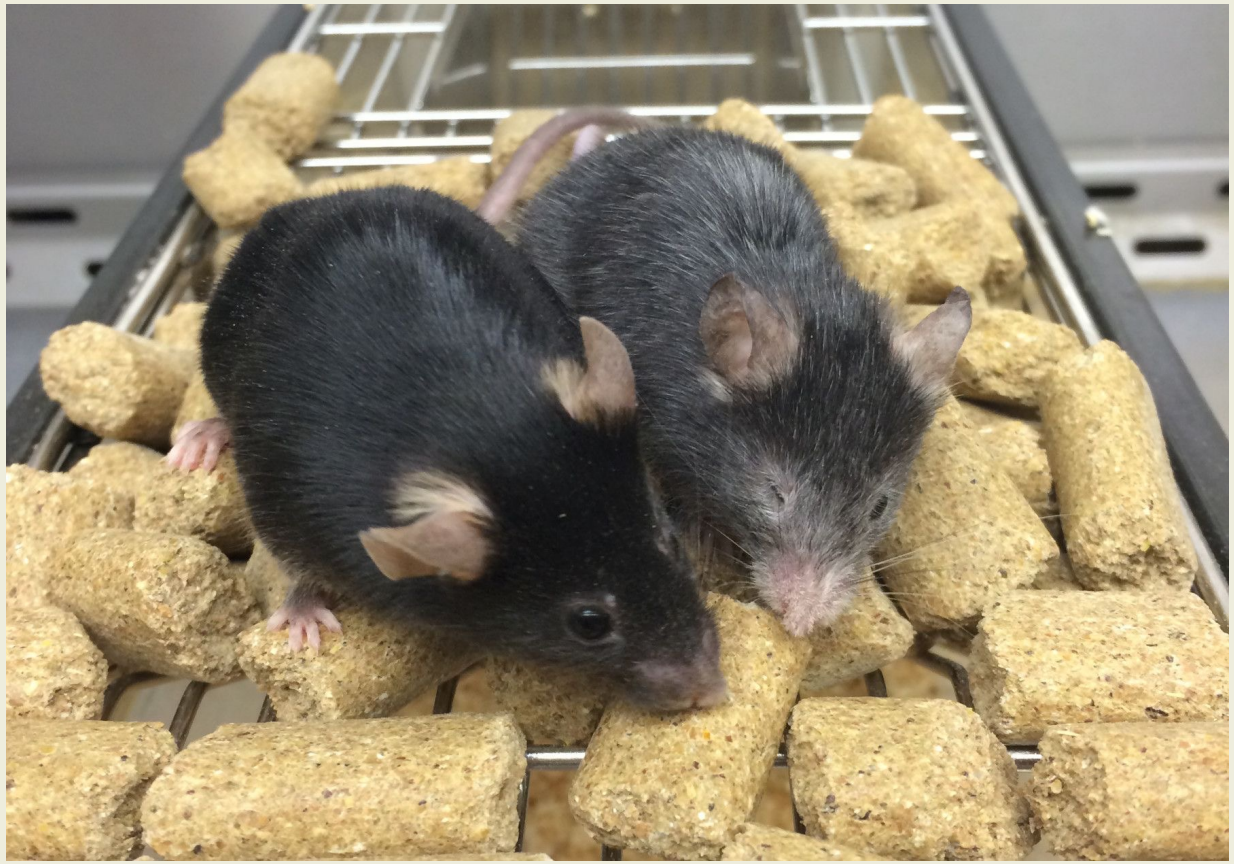
- CR always works
  - Multiple studies with no effect or deleterious effect
  - Depends on
    - Sex
    - Genetic background
    - Age on onset
    - Dietary formulation
    - ????



Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. Science. 2021 Nov 19;374(6570):eabe7365; Epub 2021 Nov 19.

Fictions of Anti-aging Diets

- Macronutrients are “Good” or “Bad”
  - Lifespan extension shown with
    - Decreased calories
    - Decreased carbohydrates
    - Decreased protein
    - ↑ or ↓ specific amino acids



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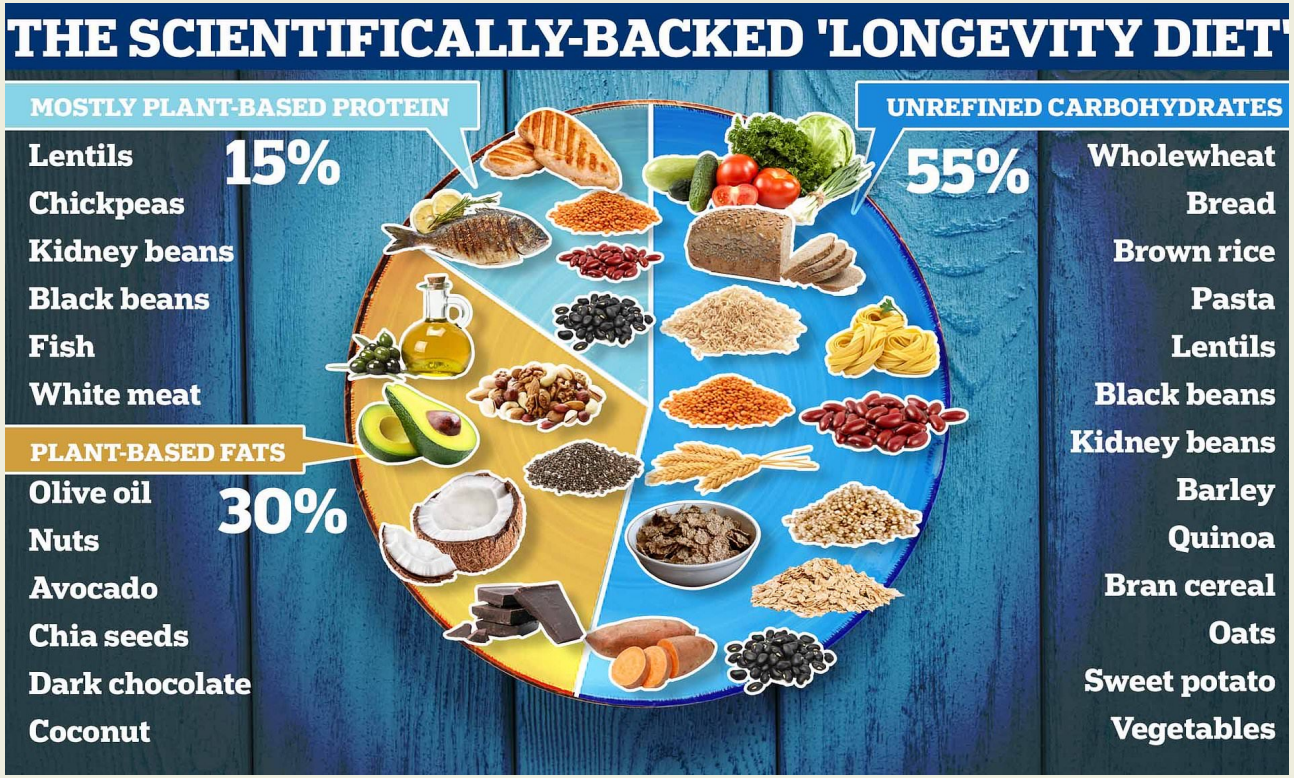
Fictions of Anti-aging Diets

- Diet X Extends Lifespan & Healthspan
  - Limited “real world” evidence
    - species
    - diets
    - populations

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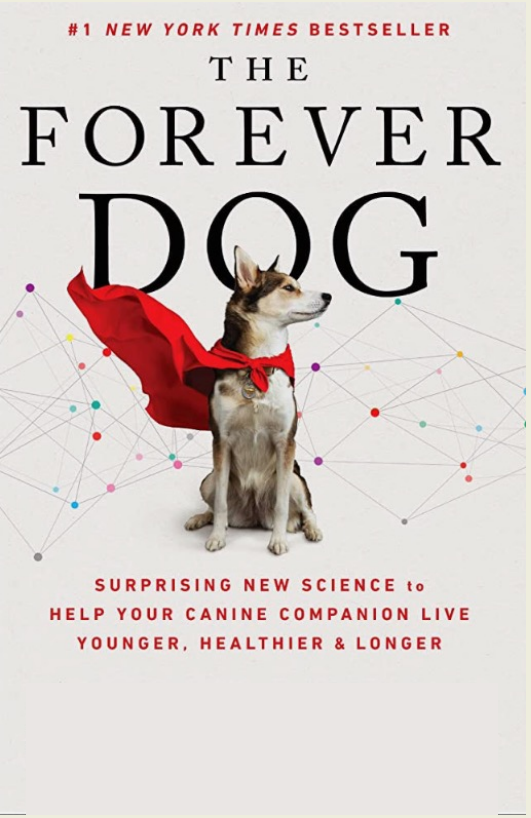
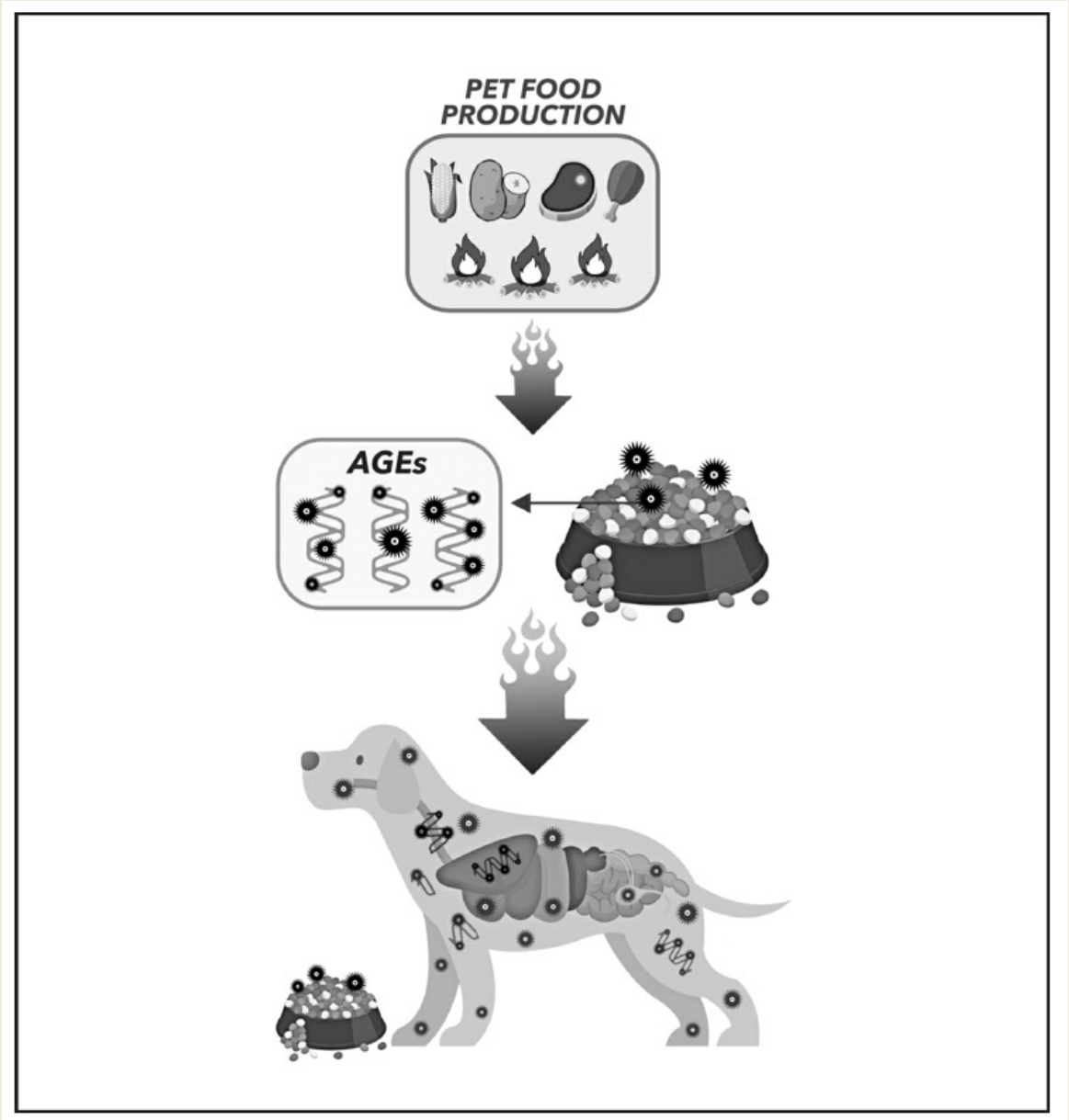
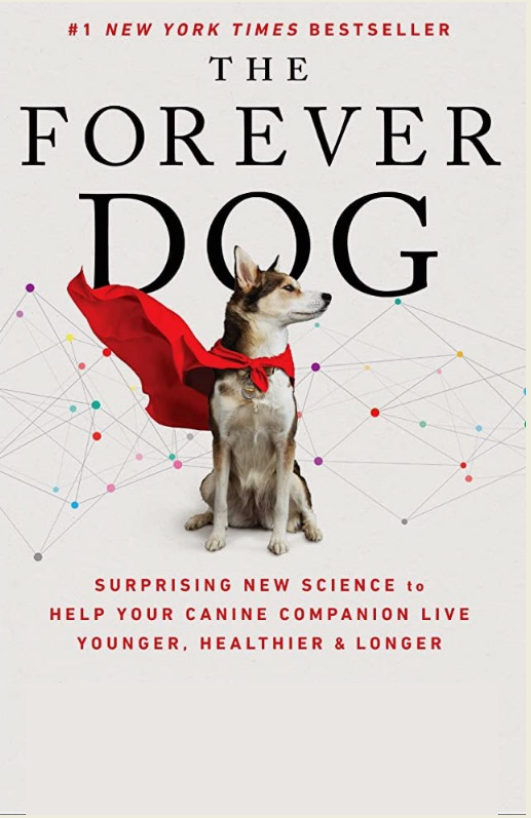
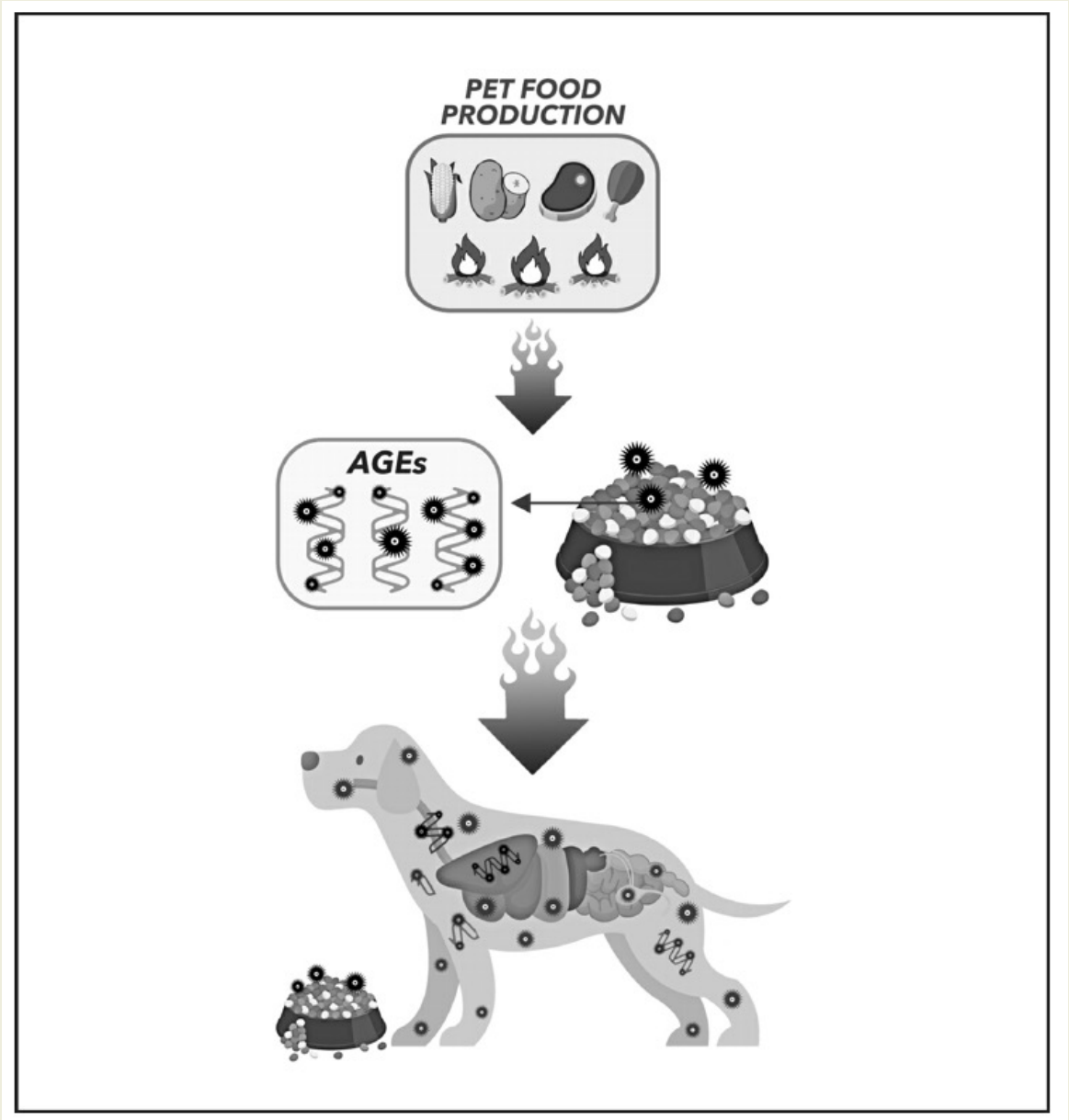


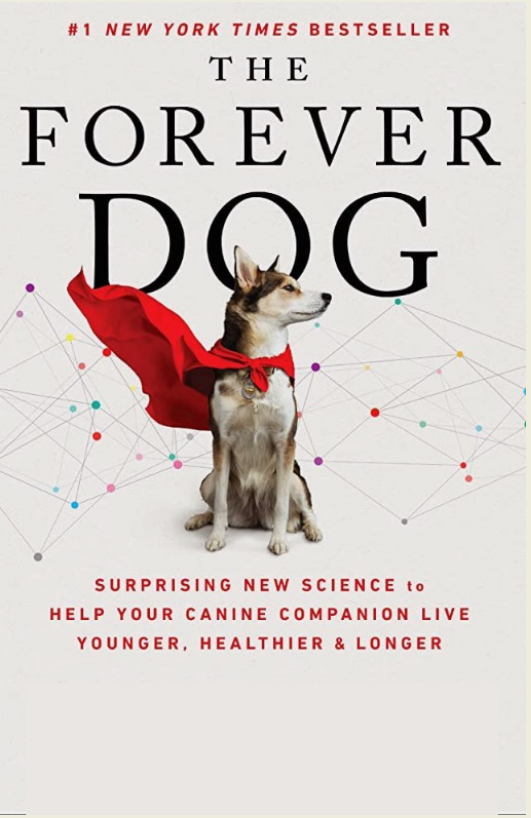


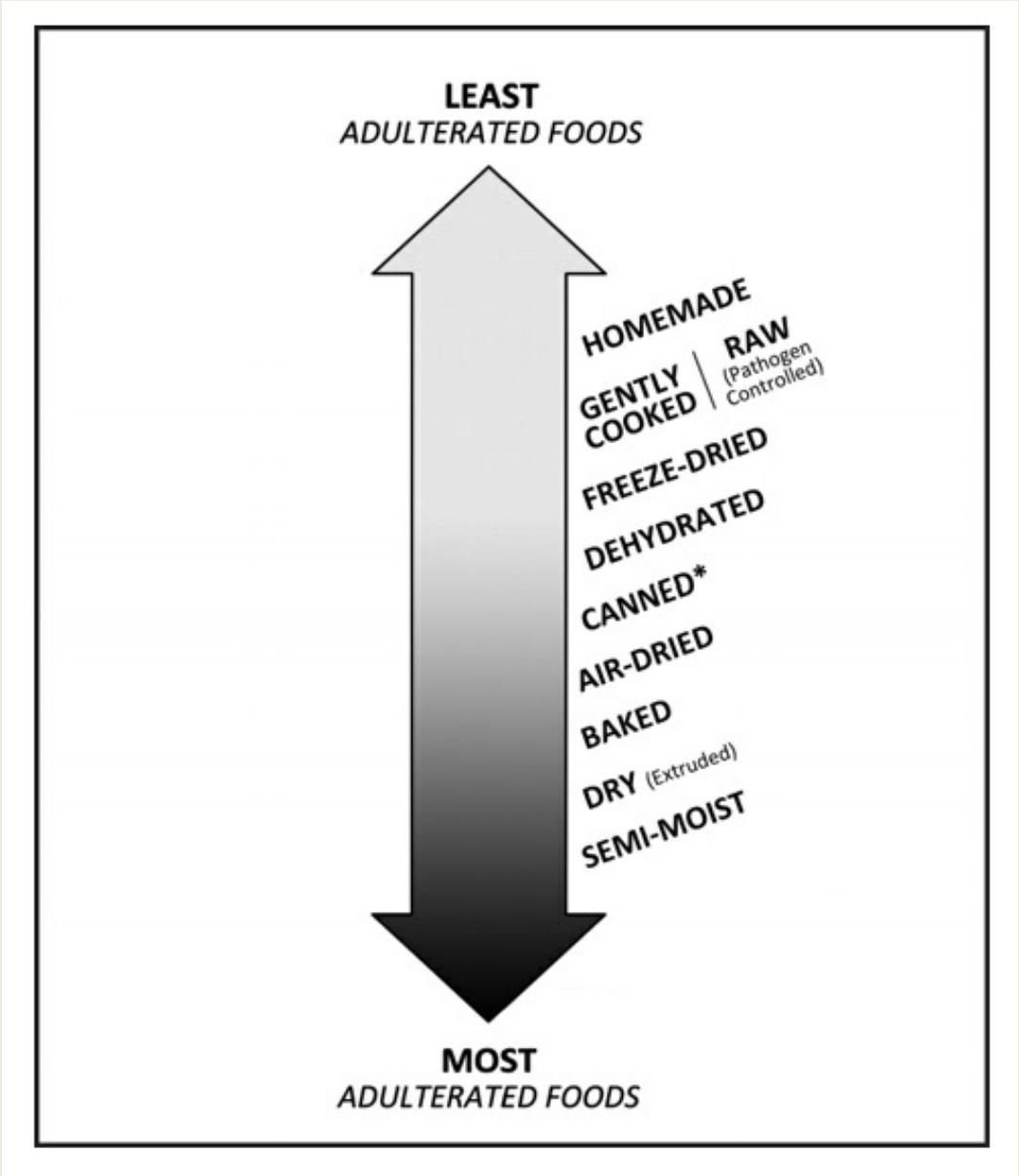
"By some measures we've witnessed a decline in canine longevity…Although many dogs are indeed living longer, like people, many dogs are dying prematurely of more chronic disease than ever before."



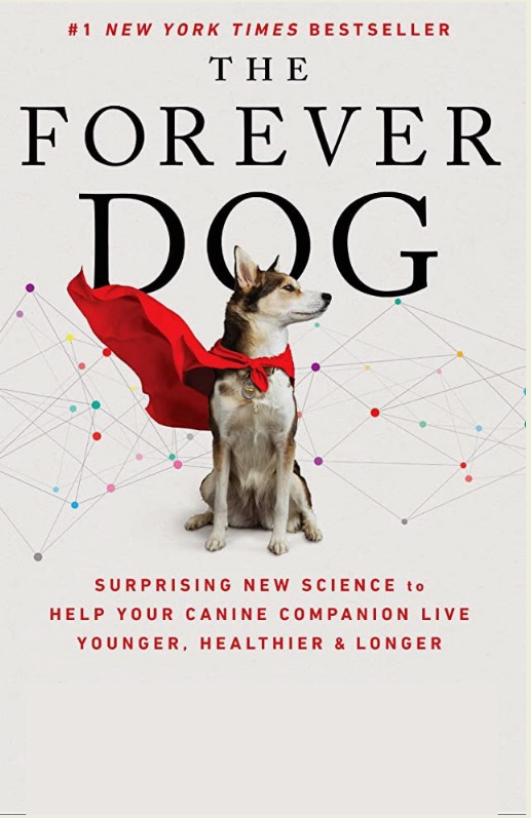


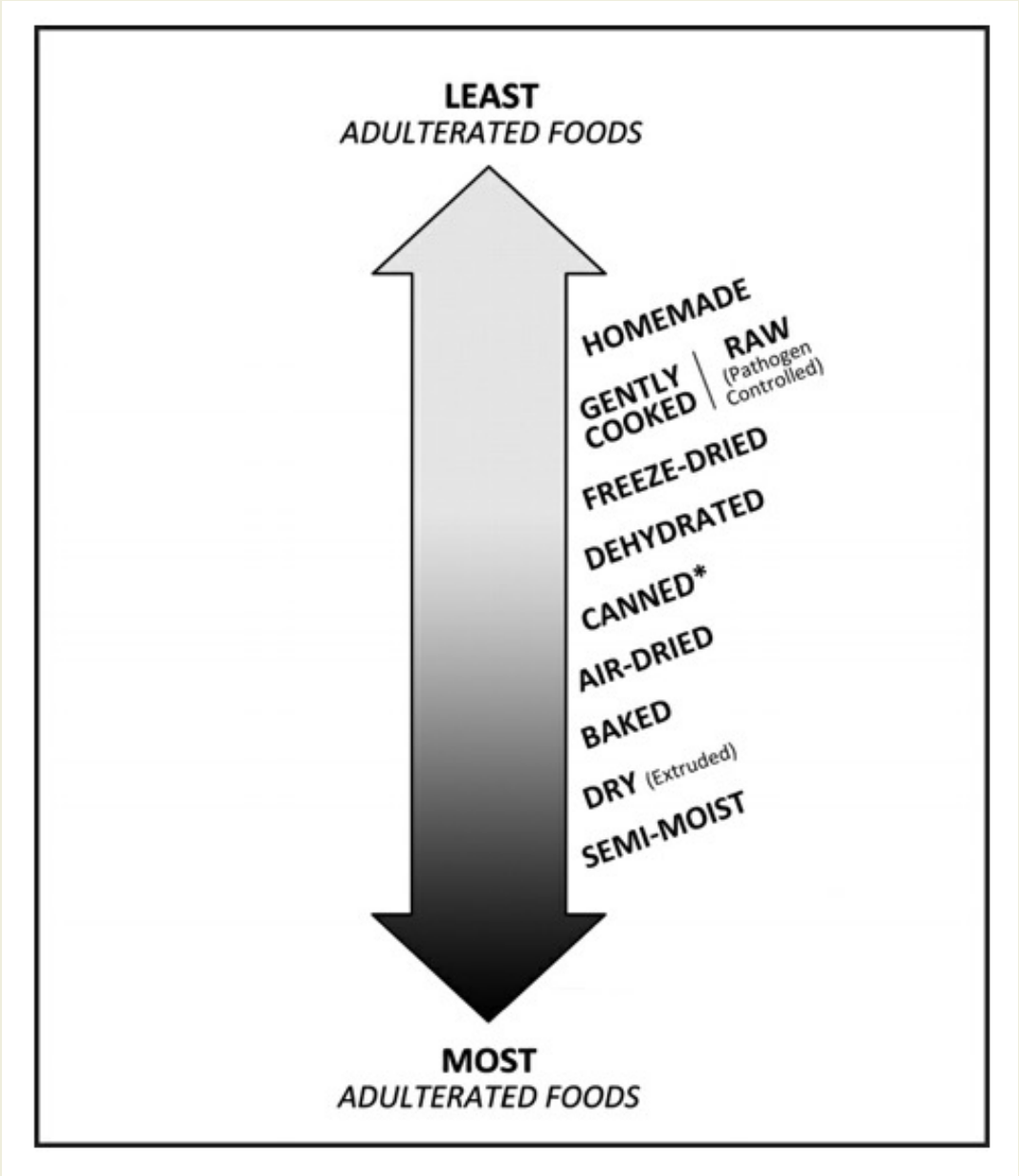
“Certainly their health span has diminished. A dog’s life is not as happy as it used to be.”





"While there aren't any lifetime studies comparing dogs that eat one **ultra-processed diet** versus a variety of less-processed foods from birth to death, common sense tells us something is wrong with the nutrition picture Big Pet Food has painted for us."



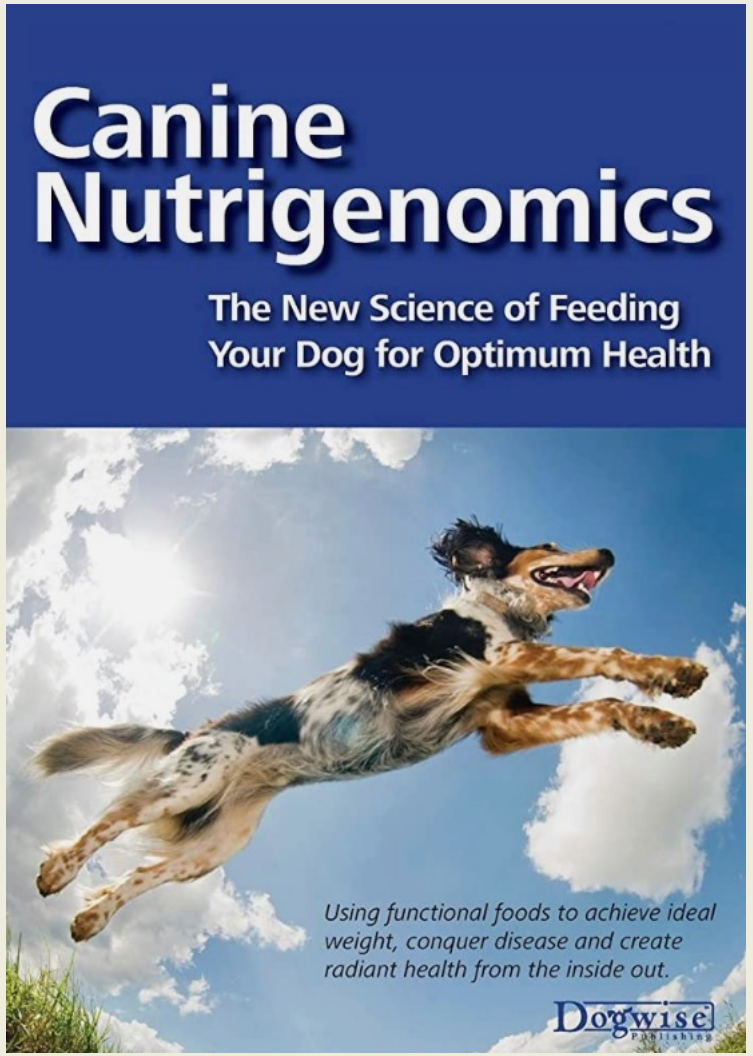


"The average bag of dry dog food contains ingredients that have been high-heat processed at least four times; **it is literally dead food.**"

“pro-inflammatory ingredients such as …**GMO foods**”

“Low-grade autoimmune reaction to **gluten** can trigger a wildfire of chronic inflammation that affects every organ system in the body. It can even create an immune response that causes subclinical brain inflammation, resulting in age-related dementia.”

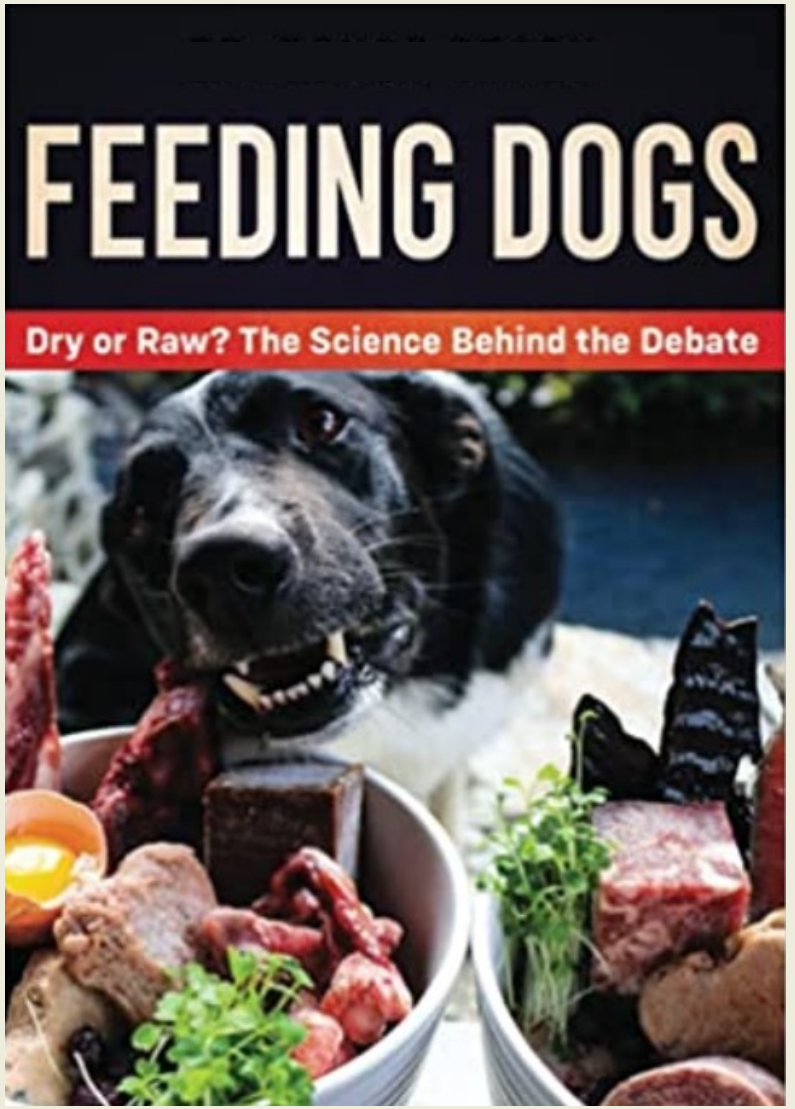
”The menacing powers of corn, wheat and soy go even further than you might imagine.”



"Cancer will play a role in nearly half of canine deaths today with older dogs more likely to get it. This is somewhat as you would expect following a life of **high carbohydrate, ultra-processed food products**, not to mention the copious amounts of **chemical parasite control** and **annual boosters**"

"The [pet food] industry is little more than a profitable dumping ground for the world's food waste…chronic illness in pets is at an all-time high…you pay with your money and your pet pays with his health."

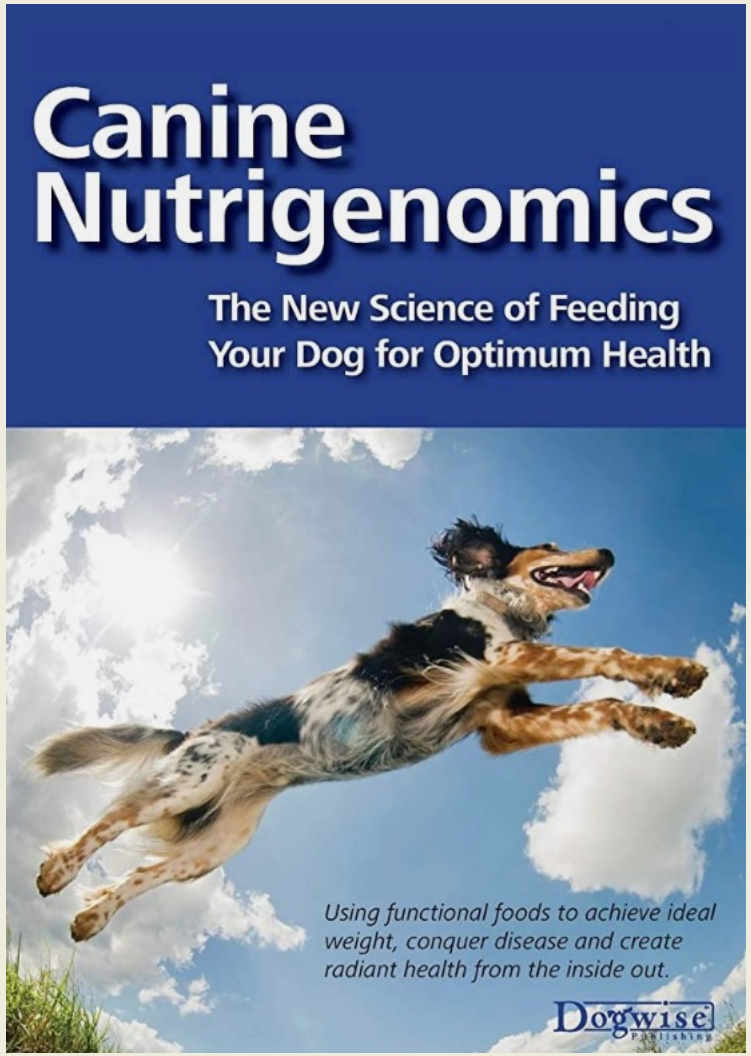
"Obesity and diabetes are terrible, chronic diseases that will lay waste to their health…It will shorten their lives and cause significant stress…We, their guardians, are **causing it by feeding them the wrong food**."



“Kibble is the least nutrigenomics-friendly choice to feed your dog.”

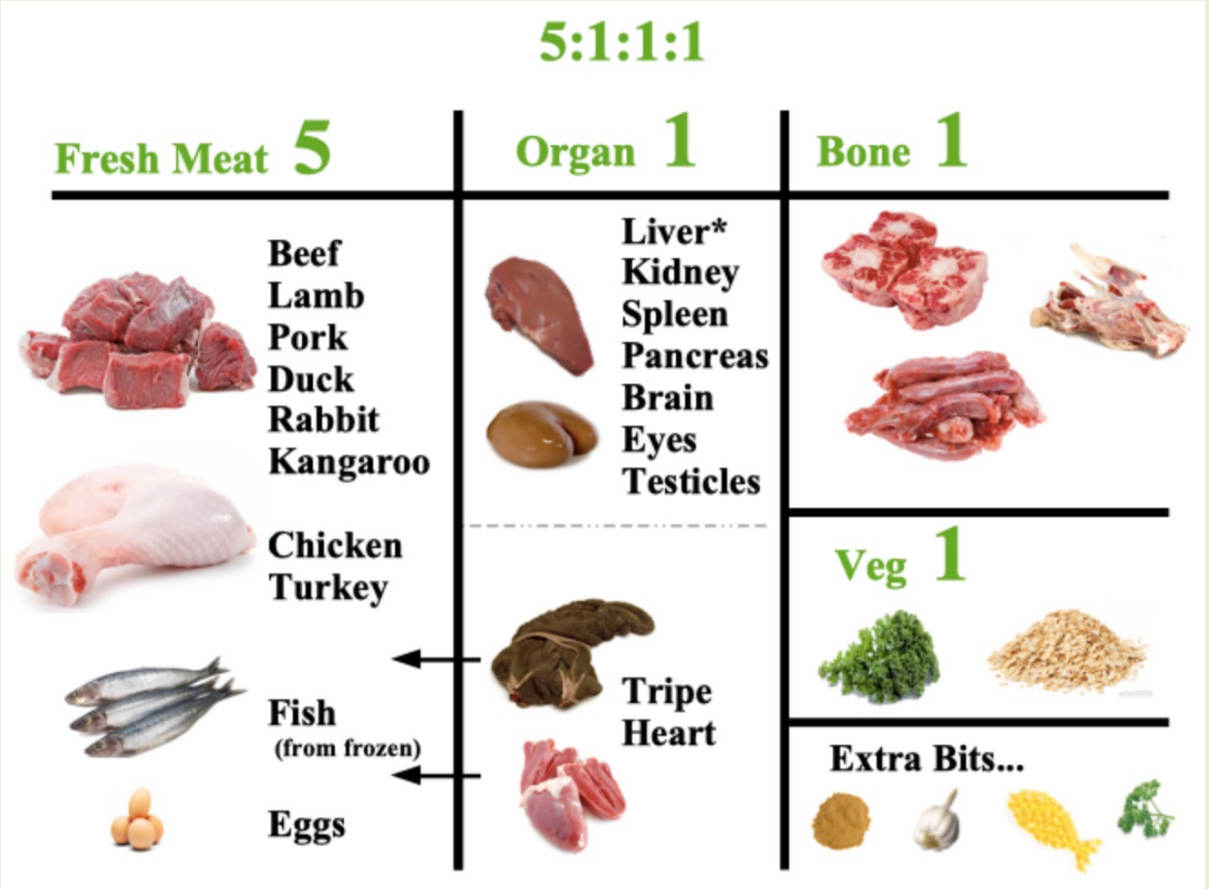
“**Raw foods** are in keeping with the principles of nutrigenomics for several reasons, including increased bioavailability of nutrients, high quality amino acids, typically no chemical additives and lesser propensity to cause food allergies.”

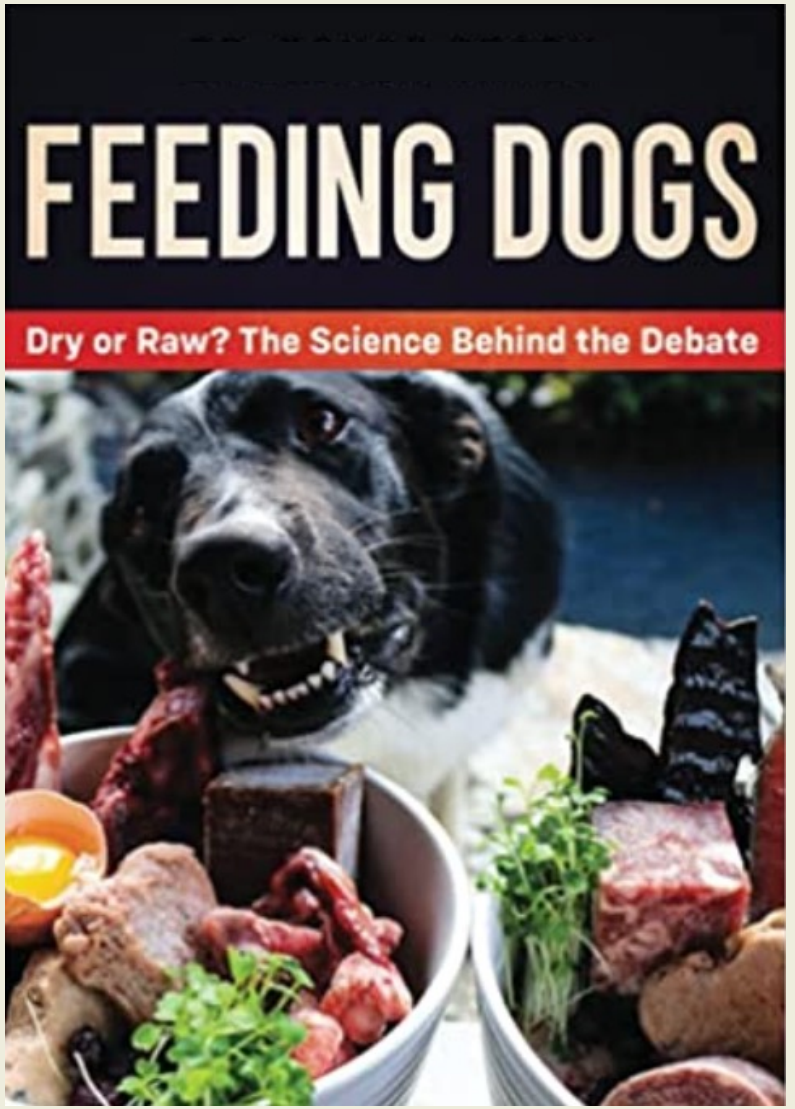
“Many respected holistic veterinarians…have witnessed first-hand the health and vigor of dogs and cats fed raw diets: these animals just “shine” in all respects.”

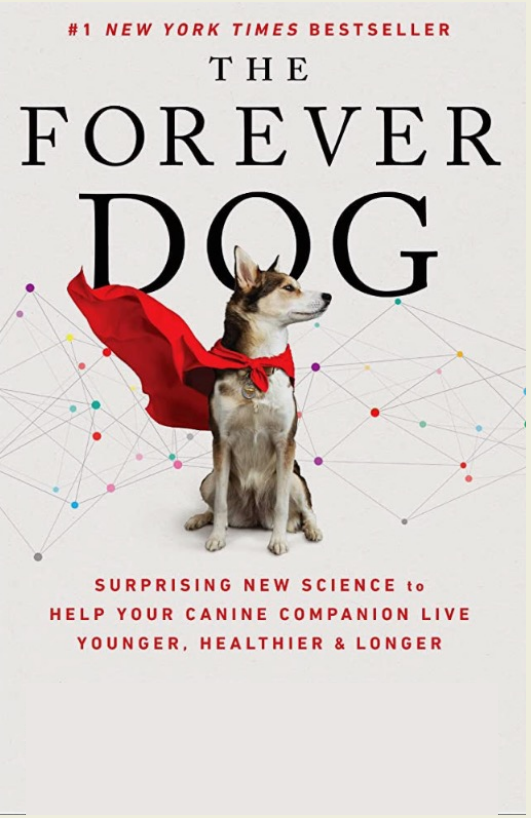


“If you are the owner of a dog breed at risk of cancer, the best diet is one **entirely free of carbohydrates**…This is the **keto diet** humans are now embarking on.

“Dogs are healthiest, certainly happiest, when fed upon a fresh, species-appropriate diet…a diet of **raw, unprocessed meat and bone.**”





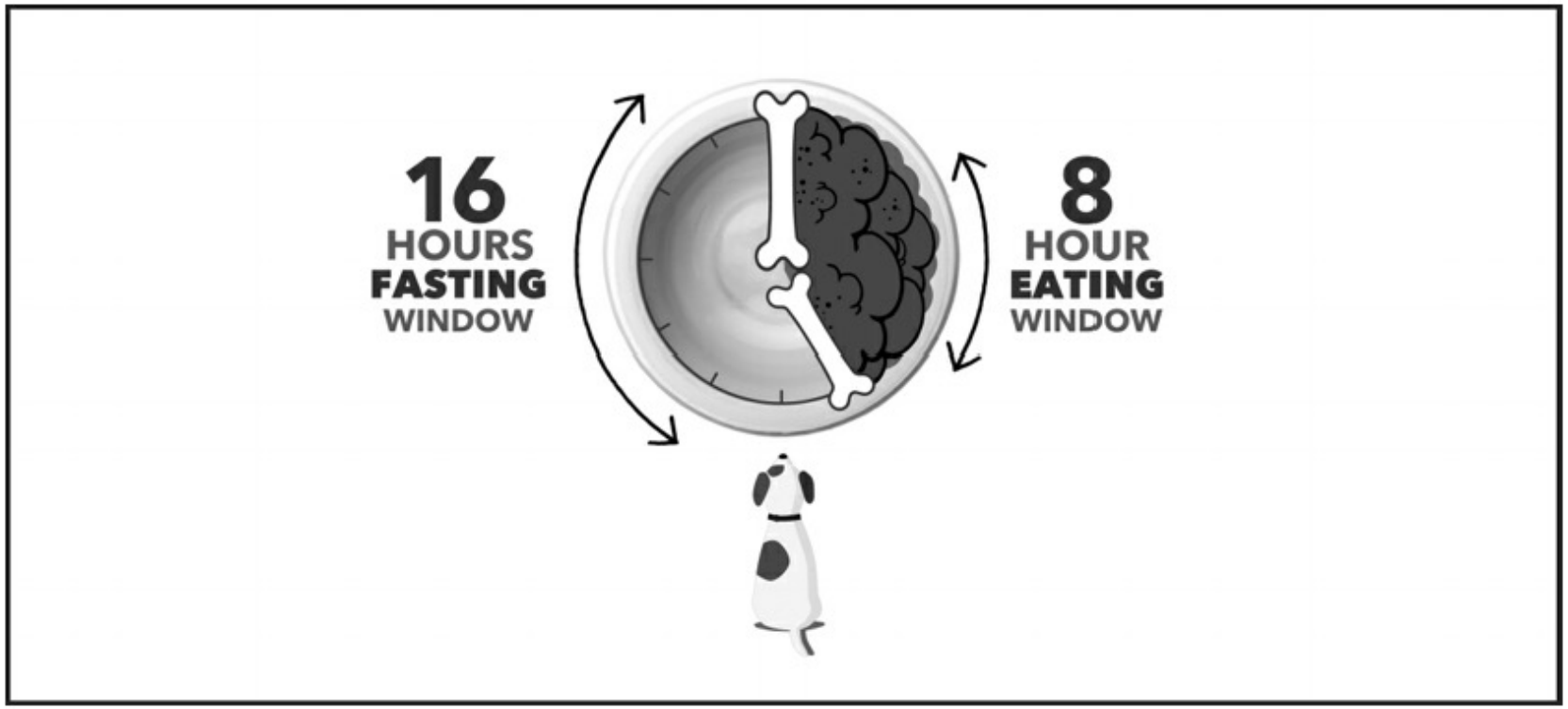


Adulteration Math Results

Good: *previously processed* ingredients blended together, and *heat processed once* (many dehydrated foods).

Better: *raw, fresh* ingredients blended together and freeze-dried or high-pressure pasteurized (HPP), as well as raw fresh ingredients blended together and *no-heat or low-heat processed* once (many raw meat dehydrated foods and gently cooked foods).

Best: *raw, fresh ingredients* blended together and served, or frozen (*no heat process*) to be eaten within three months (homemade food, commercial frozen raw food).




The Way Forward

→ Next Steps

- Further investigation of aging mechanisms
- Target-species pre-clinical research
- Clinical studies
  - Validated endpoints
  - Dietary interventions
  - Pharmaceutical interventions

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