I’ve Collected Blood, Now What?

Incorporating Geroscience into Clinical Research

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Overview

- Modeling Physical Frailty and Resiliency
- Feasible Measures of Physiology and Biology
- Inflammatory/Immune System Measures
- Suggested Guidelines

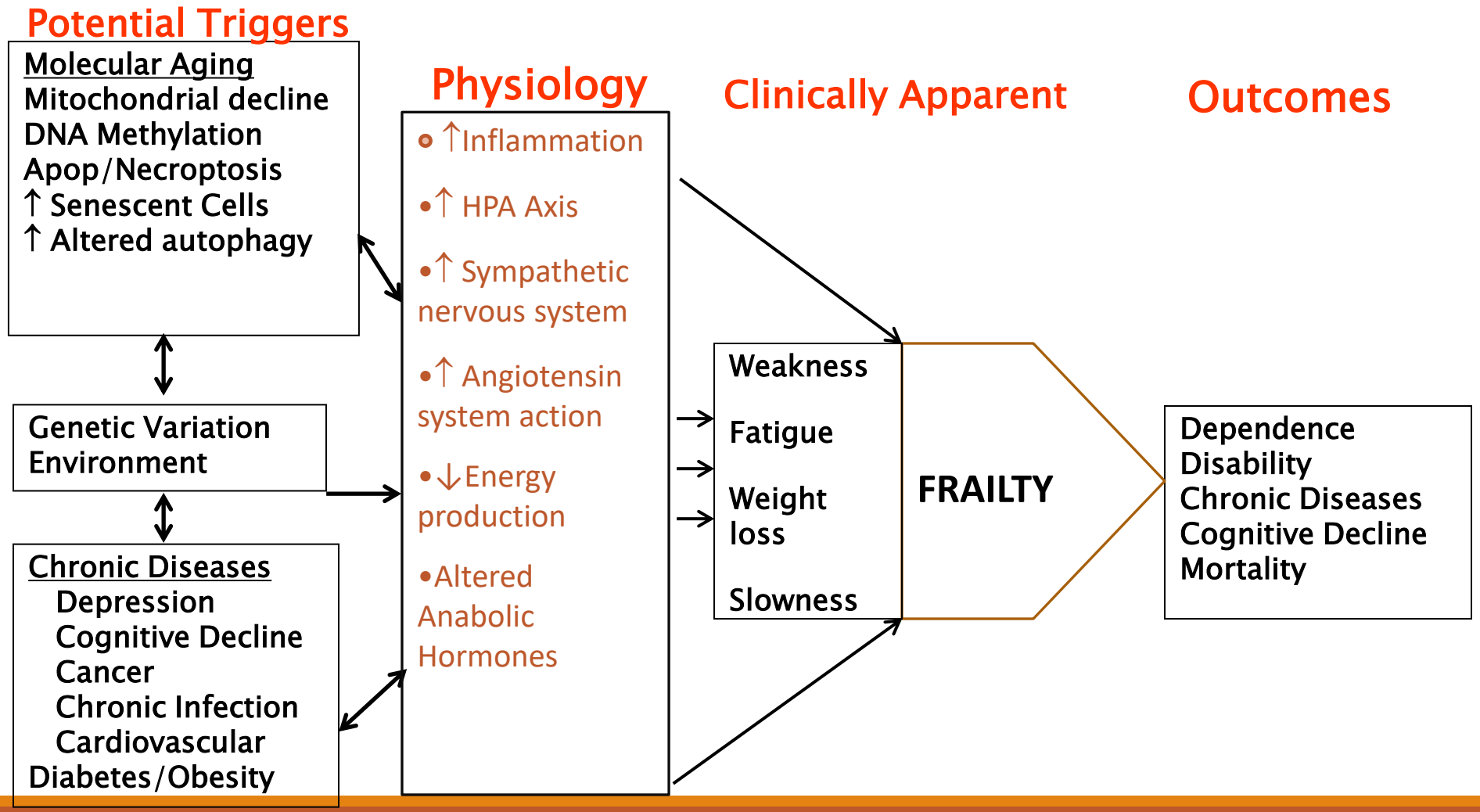
Scientific/Gerontological Models

Physical Frailty

Physical Resiliency

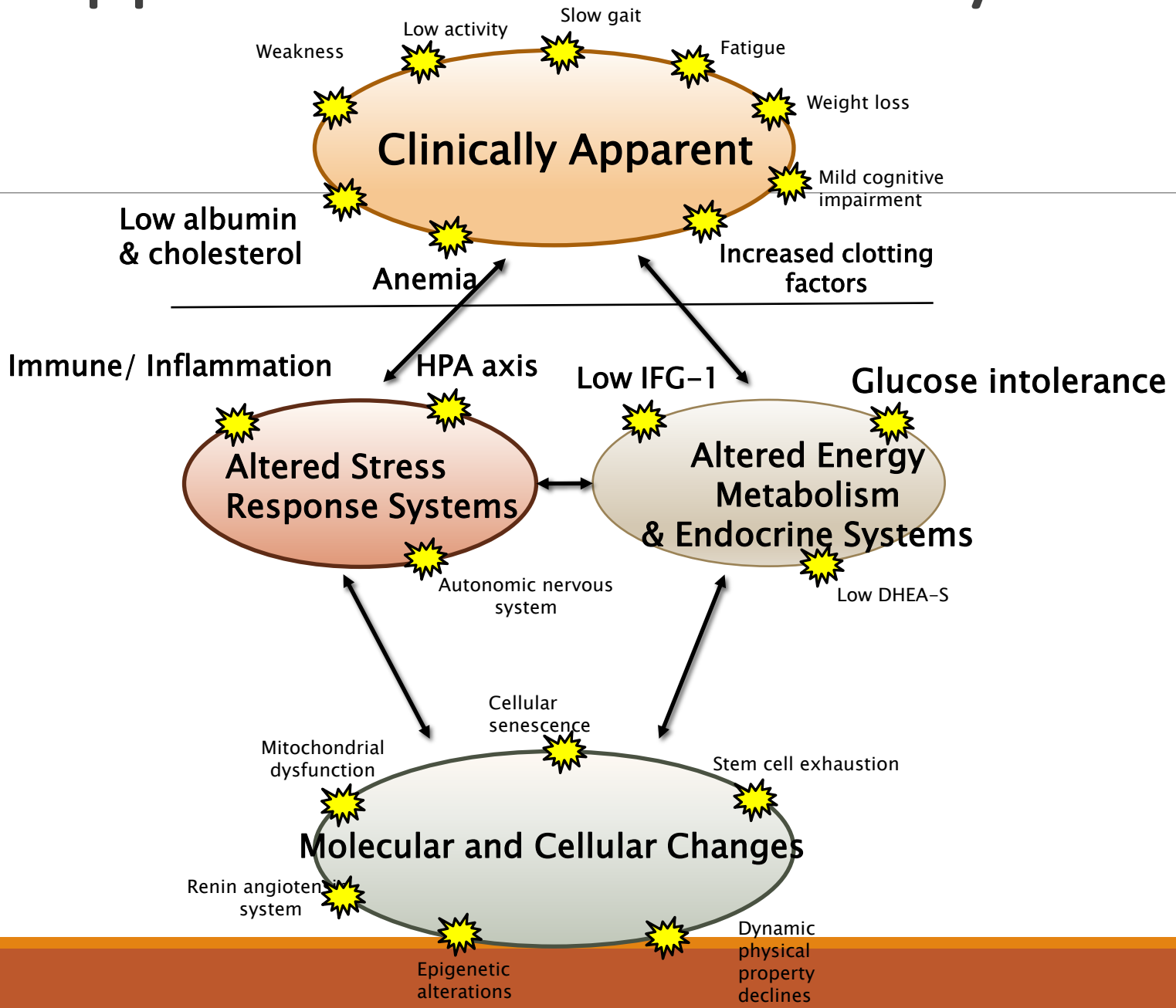
Chronic Inflammation

Complex Pathway to Physical Frailty



Walston J, 2016

Clinically Apparent vs. Invisible Frailty Measures



Biomarkers from Stimulus-Response Experiments in Physical Resiliency

- ACTH Stimulation
- Diurnal Salivary Cortisol Profile
- Oral Glucose Tolerance Test
- Holter Monitoring
- Dynamic ex-vivo response of immune cells
- Orthostatic Blood Pressure

CI Definition

Chronic inflammation (CI) is a heterogeneous, low grade activation of the innate immune system that remains ‘on’ after activation

Acute inflammation is high grade activation of innate immune system that targets specific acute injury or illness and shuts down after acute condition resolves

Consequences of CI in Older Adults

Worsening Chronic Disease States

Functional decline

- Sarcopenia, fibrotic tissue replacement
- Satellite Cell Decline

Cognitive decline

- Neurodegeneration and MCI

Physical Frailty

- Poor response to vaccines
- Altered Stress Response Systems and Energy Metabolism

Intrinsic or Age-Related Etiologies (Geroscience)

Necroptosis-related Cellular Debris (immune modulating)

Senescent Cells (fat, fibroblasts)

Altered Immune System (senescent, clonal cells)

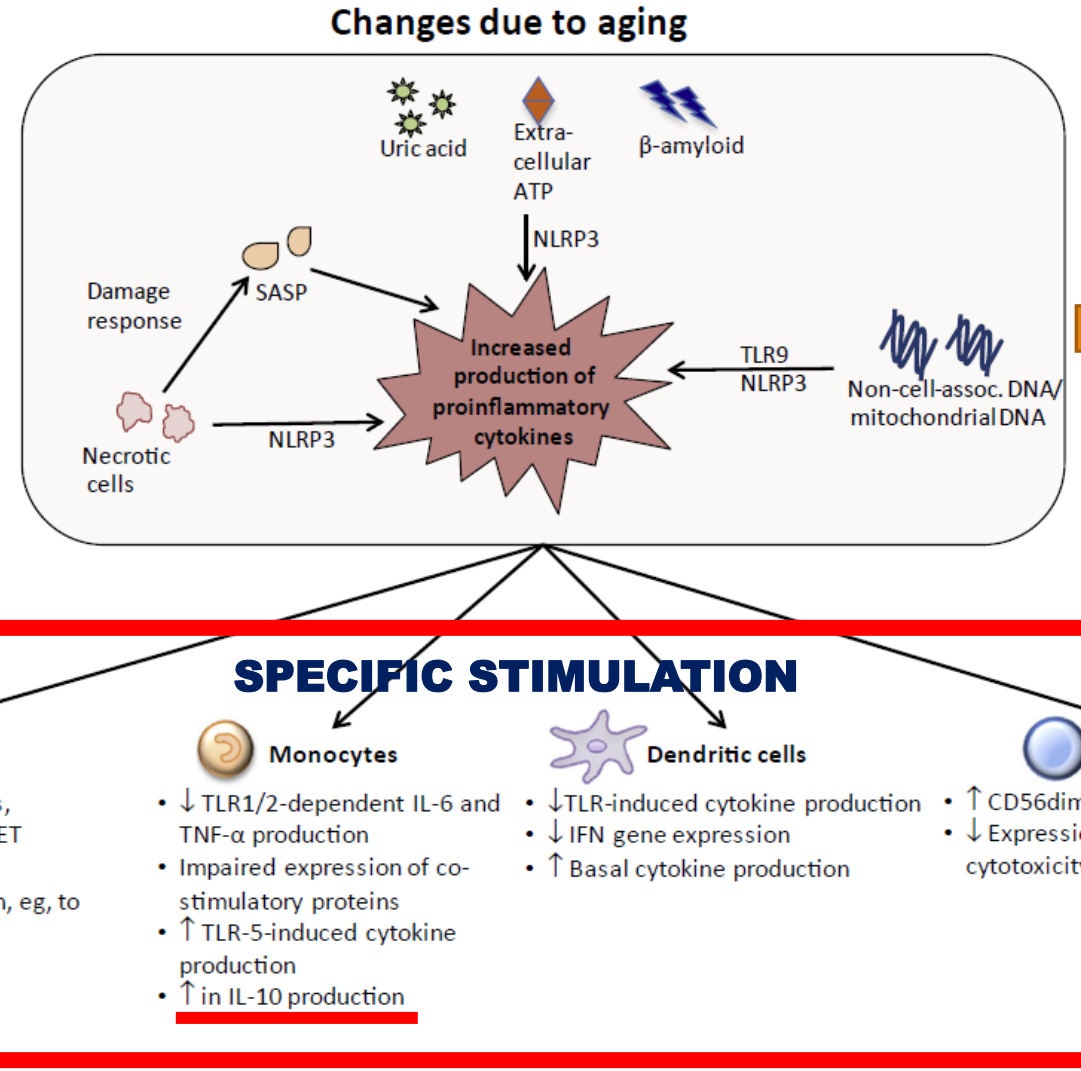
Altered Gut Wall and Microbiome

Gene Variation (contributory or preventative)

Mitochondrial damage and oxidative stress

Intrinsic (Ageing)Alterations in the Innate Immune System

Increased activity at the basal state



Chronic Inflammation

Bandaranayake and Shaw Clin Geriatr Med 32 (2016) 415–432

Best Serum Markers of CI to Date

1. **TNF-alpha R1**** (*validated, less variable, biologically relevant)
2. **IL-6 **** (*validated, quite variable with illness)
3. **CRP** (utilized in clinical practice, distal signal, more vascular)

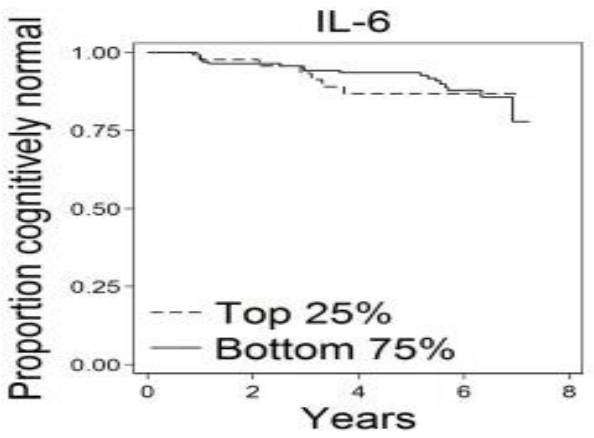
** cytokines have good evidence of consequential biological activity

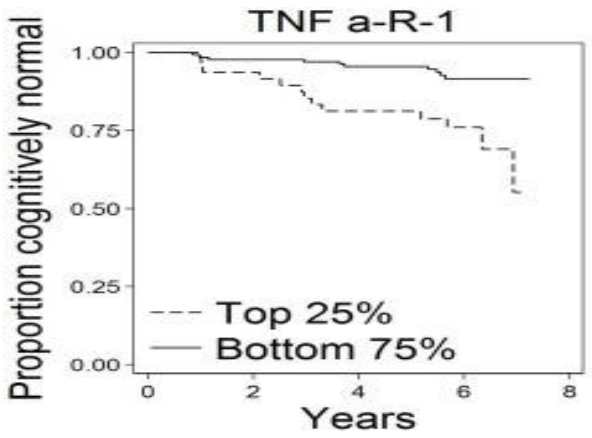
Cytokines and Mortality over 10 Years in CHS

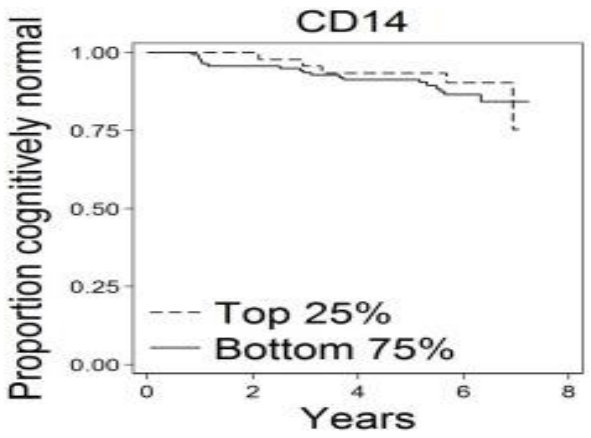
Parameter	Chi-Square	Pr > ChiSq	Hazard Ratio
logCRP	72	<.0001	1.22
logIL6	287	<.0001	1.44
logTNFRI	274	<.0001	1.48
logIL18	24	<.0001	1.12
logIL1RA	56	<.0001	1.19
age	772	<.0001	**1.80**
WSS	281	<.0001	1.47
PCS	237	<.0001	1.43
IIS	**433**	**<.0001**	**1.64**

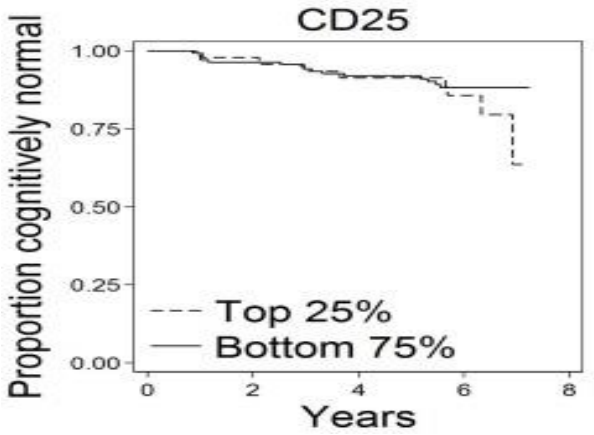
Varadhan R et al, JGMS, 2014

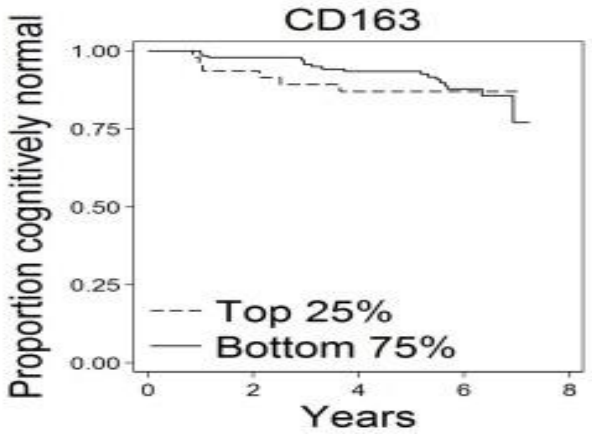
Chronic Inflammation and Future MCI











Gross A. et al, 2019, Frontiers in Neurology

IL-6 and Multisystem Dysregulation

Rhesus monkeys injected with low dose IL-6 developed multisystem changes

- 10% lean body mass decline by DEXA within 30 days
- Anemia & osteopenia
- Decreased albumin & cholesterol
- Increased CRP, alkaline phosphatase

Binkley, NC, et al. 1994 and Ershler & Keller, 2000

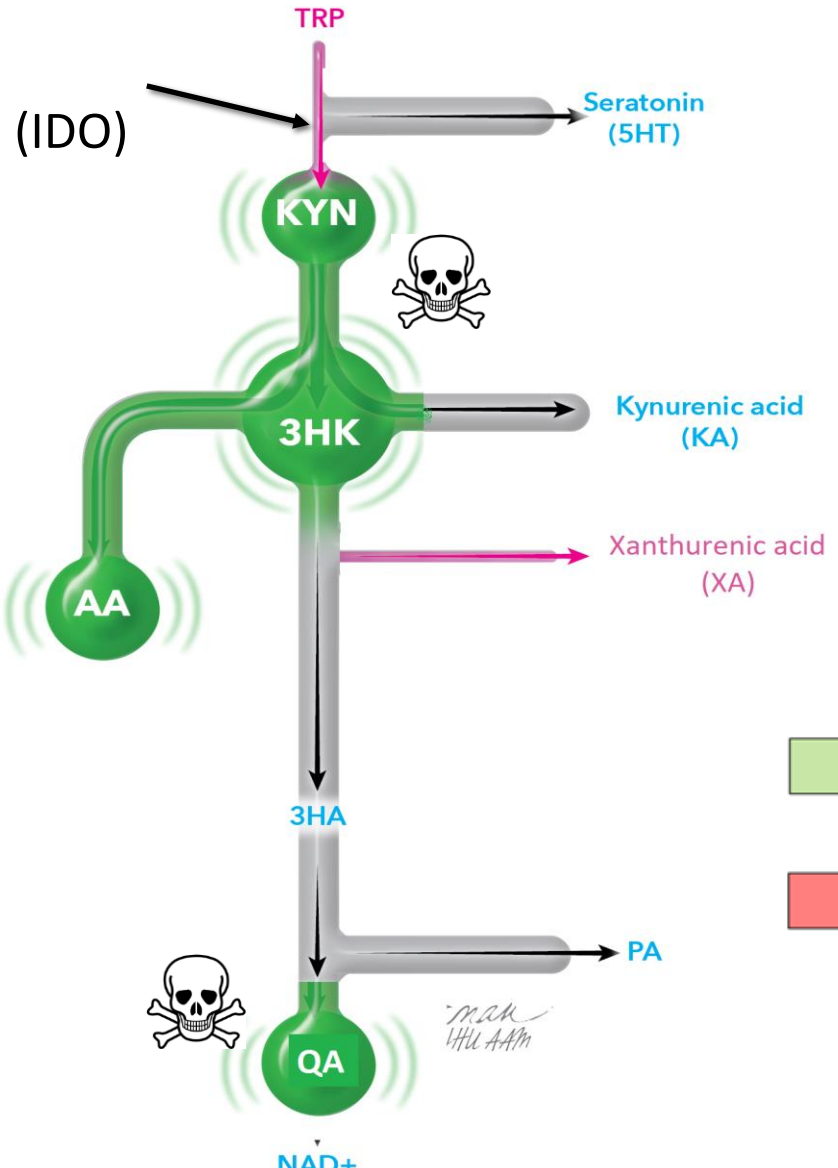
Chronic TNF-Alpha R1

- Contributes to necroptosis signaling and DAMP release
- DAMP drives further inflammatory pathway activation
- Accelerates cell loss in frailty

CI and Neurotoxic Tryptophan Metabolites: Sarcopenia and Frailty?

Indoleamine 2,3-dioxygenase (IDO)

↑ Chronic Inflammation
IL-6, TNFα, INFγ



Increased relative to control

Decreased relative to control

Westbrook R and Chung T, JCI Insights 2020

Summary

- Use Modeling to Develop Clinical Connections to Aging Phenotypes and Measurement Priorities
- Consider Physiology and Biology Measures
- Think Feasibility and Tight Focus for Present Projects
- Absolutely Store Samples for Broader Future Opportunities
- Think Intervention Development!! (feasible diagnostics, treatment monitoring, in addition to clinical measures)

Acknowledgments

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Characterizing Resiliencies to Physical Stressors in Older Adults: A Dynamical Physiological Systems Approach, UH3AG056933

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