A4M | MEDICINE REDEFINED

CLINICAL WEIGHT MANAGEMENT

Certification Program

IPS THE PREMIER EDUCATIONAL RESOURCE FOR SAFE & ADVANCED PEPTIDE THERAPY

EDUCATIONALLY PARTNERED WITH A4M

Weight Loss: A Practical and Evidence-Based Approach: Introduction

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No actual or potential conflict of interest in relation to this program/presentation”

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METABOLISM

The sum total of all the chemical reactions ***driving how you feel today*** *and creating the chemistry* ***moving you toward future health***

Metabolic Networks

Understanding the "disruptors" to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

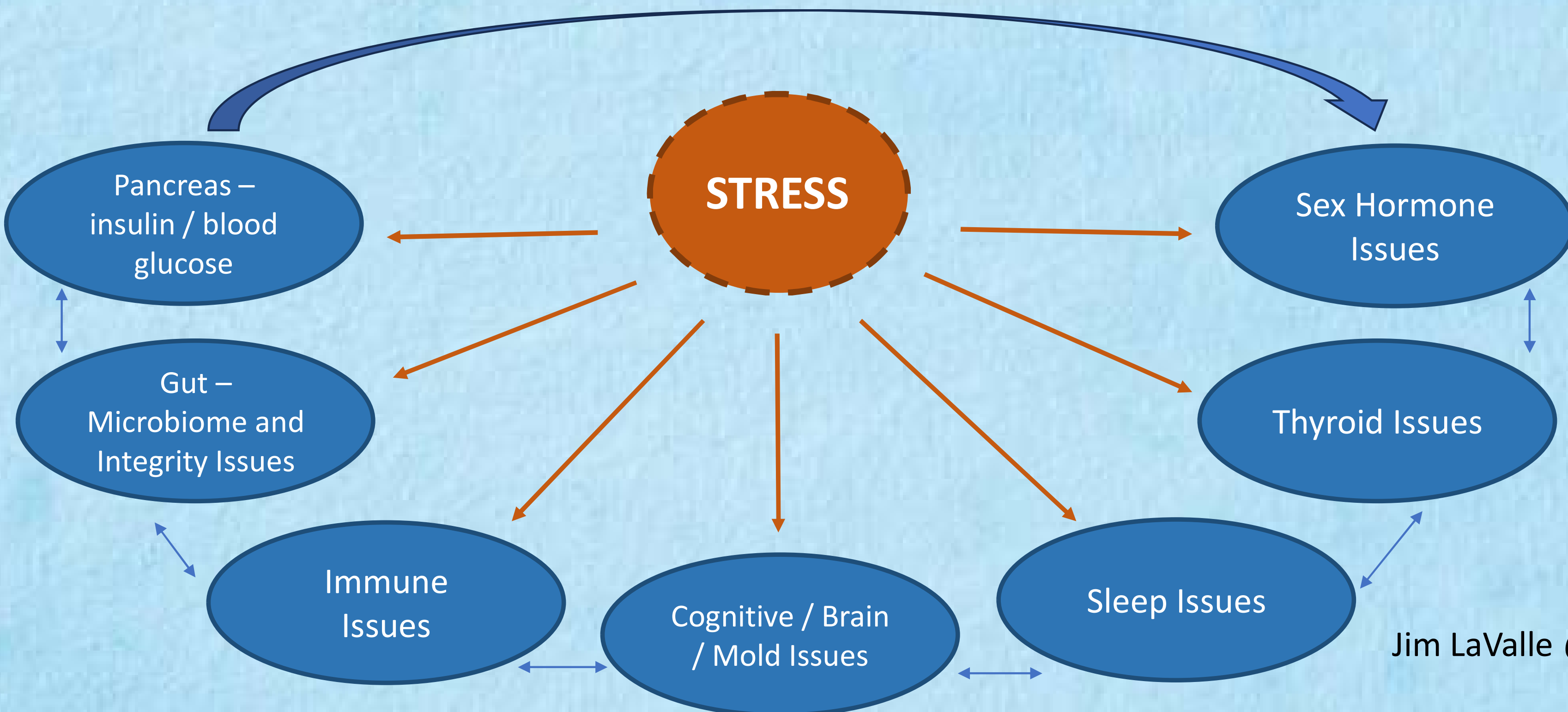
Key Tenants of

Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- **Glucose / Insulin Regulation**
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Burden
- Individuality

A Systems Biology Approach

Optimizing Inter-relationships of organ systems



Jim LaValle @ jimlavallle.

Obesity Background

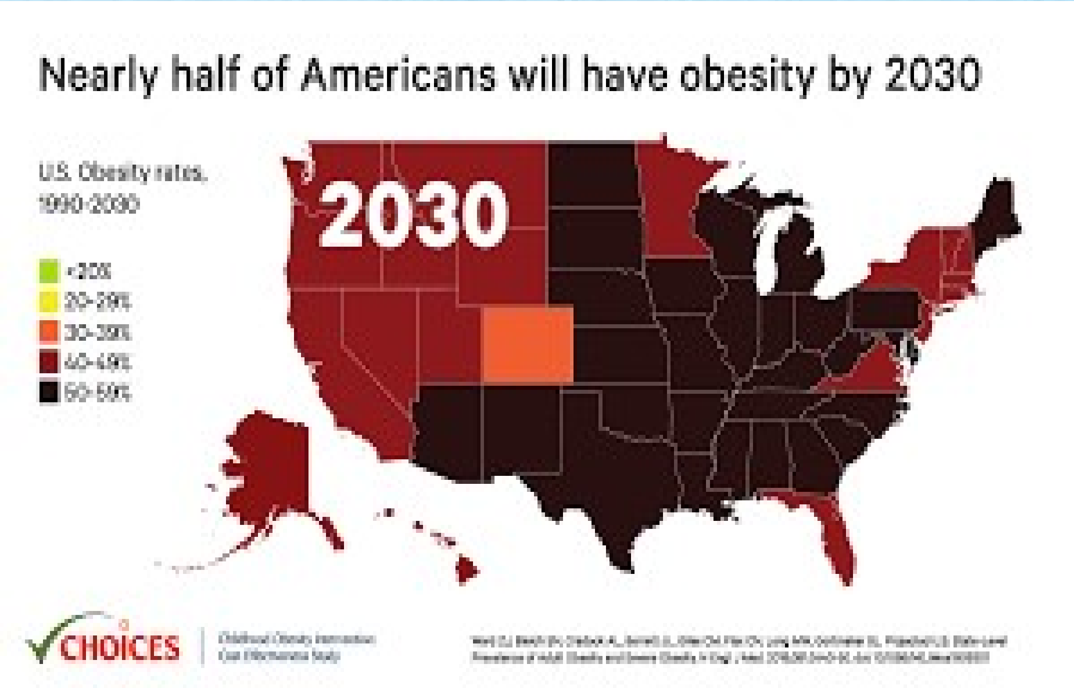
- Chronic disease of multifactorial origin
- Develops from the interaction of social, behavioral, psychological, metabolic, cellular, and molecular factors
- World Health Organization (WHO) defines obesity as a body mass index (BMI) > 30 and defines overweight as with a BMI of 25

Weight Loss Statistics

- Despite huge expenditures and participation in weight loss programs, only 5 - 10% achieve sustained weight loss
- (90% gain weight back in 5yrs or less)

- Many experts concluding calories in vs. calories out - not the whole story

- Half the US population will be obese by 2030



Weight Loss - New Approaches Needed

- Weight Loss - conventional approaches still focusing entirely on “calories in- calories out” and is . . .

- Not evaluating all factors that affect the equation.

- NIH - 2004 issued new strategic plan for obesity

- “Leave no stone unturned” in fighting the epidemic of obesity

Diabetes Epidemic

- 2022 number of people in US w/ diabetes/pre-diabetes = 130 million
- On top of this – COVID reported to increase risk of T2D by up to 22%
- ADA estimates up to 70% of individuals with prediabetes will eventually develop diabetes

Tabak AG, et al. Prediabetes: a high-risk state for developing diabetes. Lancet. 2012;379(9833):2279-90.
Naveed Z, et al. Association of COVID-19 infection with incident diabetes. JAMA Network Open. 2023;6(4):e238866.

Weight Loss Industry

- **AMERICANS SPEND $66 BILLION ANNUALLY ON WEIGHT LOSS**
- 97 million Americans are on a “diet” at any given time
- 80% try to lose weight by themselves with no medical supervision
- Currently only 5% of people who attempt weight loss will be successful at maintaining their weight for at least 2 years.

Centers for Disease Control (CDC), 2016; www.cdc.gov

Key Disturbances That Contribute to Fat Gain

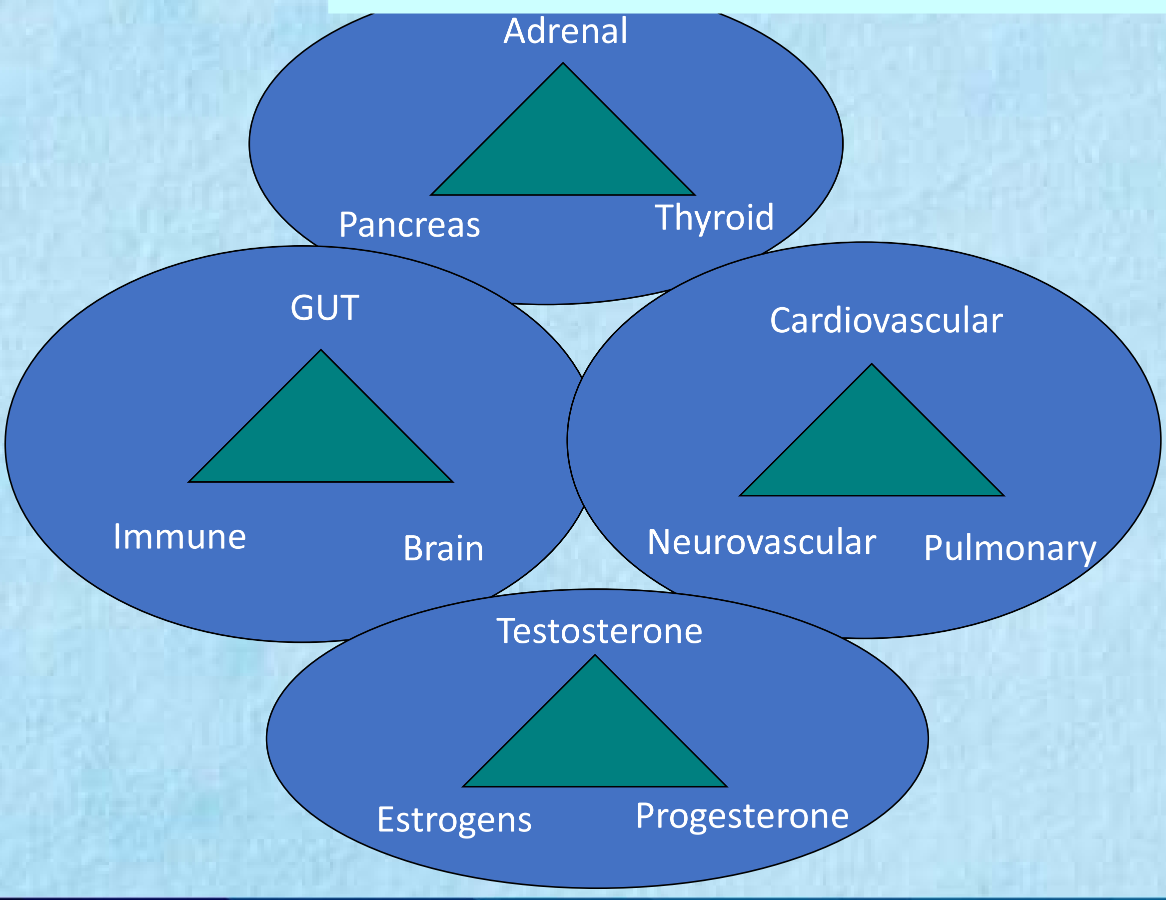
- Gut/Immune Balance
- Chronic Inflammation
- Nutrient deficiencies
- Infections – *including mold, biotoxins*
- Skewed Diet intake
- Mitochondrial dysfunction
- Cortisol – stress
- Sleep issues
- Craving – Reward - Satiety
- Low metabolic performance (thyroid)
- Intoxication / Kidneys-Liver-Lymph
- Sex hormones
- Drug use
- Genetics
- **LACK OF EXERCISE**

Studies/headlines

- Some types of fat are more problematic than others
- Belly fat and fasting insulin levels are predictors of growth hormone release
- Belly fat is the most common type of obesity associated with insulin resistance (pre-diabetes, MS)
- Non-overweight individuals who have belly fat also prone to insulin resistance and accompanying inflammation

Clasey JL, et al. Abdominal visceral fat and fasting insulin are important predictors of 24-hour GH release independent of age, gender, and other physiological factors. J Clin Endocrinol Metab 2001 Aug;86(8):3845-52.

As your Metabolism spirals downward …….



- Glucose Control less
- Inflammation signals increases
- Blood Pressure increases
- Cholesterol increases
- Belly Fat increases
- Lactic Acid Increases
- Immune System less effective
- Cognitive Capacity decreases
- Sex Drive Hormones alter

ALL LEADING TO WEIGHT GAIN

REMEMBER

Effective Weight Loss is More Than

Calories in = Calories Out

Body Composition Changes in Weight Loss

- 1/3 of US population has BMI > 30kg/m^2
- Weight loss is generally accompanied by loss of lean body mass
- In overweight people, 20-30 % of total weight loss is muscle mass
- Multiple health implications:
  - Lowered resting energy expenditure/metabolism
  - Decline in neuromuscular function / disability
  - Fatigue
  - Emotional effects
  - Poor day-to-day performance issues
  - Increased risk of injury

Willoughby D, et al. Body Composition Changes in Weight Loss: Strategies and Supplementation for Maintaining Lean Body Mass, a Brief Review. Nutrients. 2018;10(12):1876.

Body Composition Changes in Weight Loss

- Obese individuals are reported to be deficient in certain key nutrients, including:
  - Vit D, C, A
  - B1, B12, folate, biotin
  - Zinc
  - Selenium
  - Chromium
- Metabolic decline after LBM loss can result in subsequent regain in fat mass
- Important to preserve and protect lean body mass
- Focusing on body composition is essential

Willoughby D, et al. Nutrients. 2018;10(12):1876.

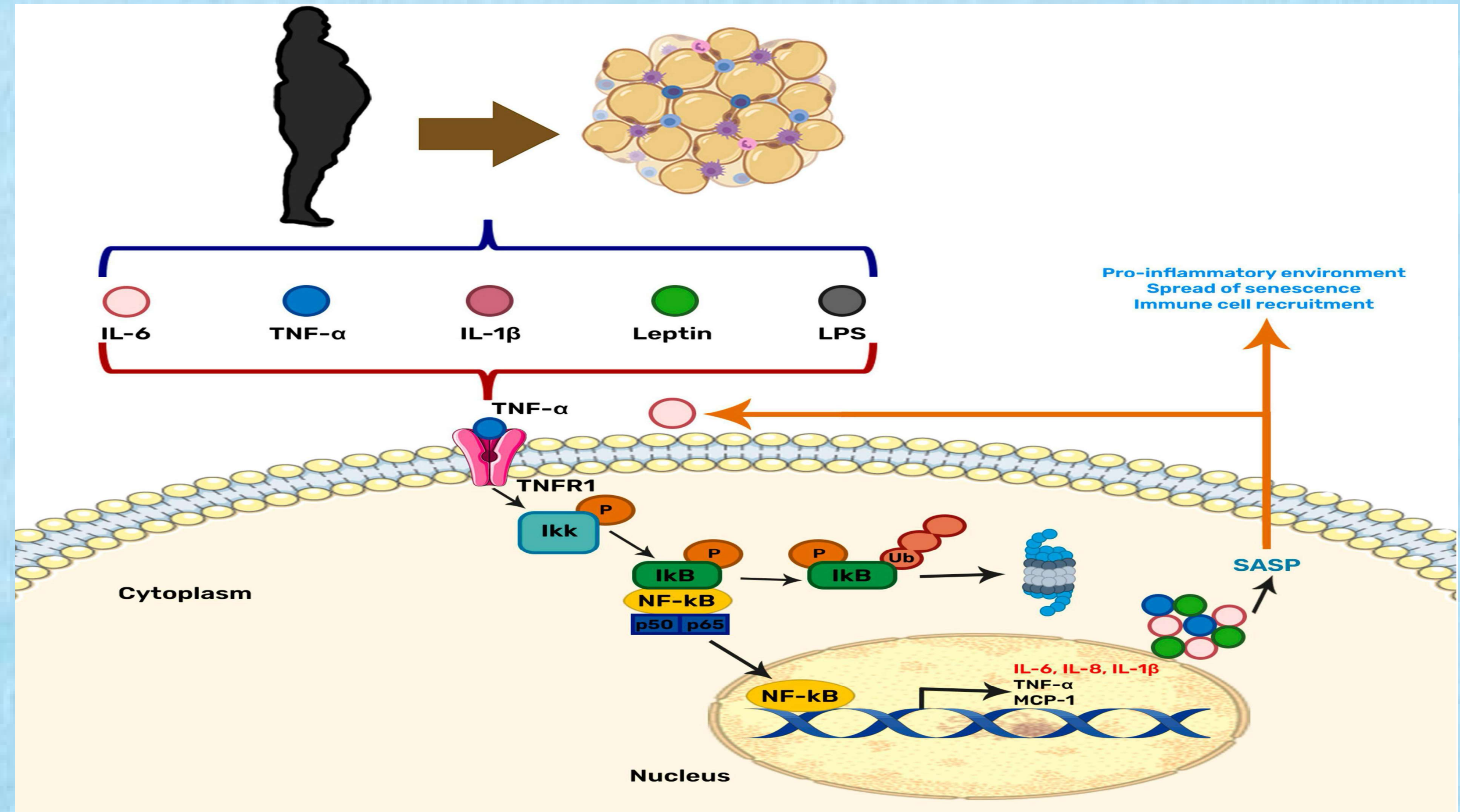
Belly Fat – An Inflammatory Organ

- Increased risk of insulin resistance
- Immune imbalances
- Increased Estrogen – estrogen dominance
- Increased Aromatase
- Androgen imbalances
- PCOS (women)
- Increased Agiotensinogen
- Decreases growth hormone production
- Increased TNF alpha - alters insulin signaling
- Increased oxidative stress - lowers Glutathione
- Increased osteoarthritis
- Increased Glycation
- Increased Isoprostanes
- Increased Interleukins, IL-6
- Increased Risk Non-Alcoholic Fatty Liver
- Increased cancer risk

As BMI approaches 30, brown/beige fat thermogenesis starts to decrease significantly

Pirola L, Ferraz JC: Role of pro- and anti-inflammatory phenomena in the physiopathology of type 2 diabetes and obesity. World J Biol Chem. 2017, 8:120-8.

Obesity-Related Inflammation and Senescence



Salas-Venegas V, et al. Front integ Neurosci. 2022;16:2022.

Weight Gain Fuels Inflammation and IR

- Adipose tissue ↑ inflammatory markers
- TNF-α, IL-6, resistin, leptin, MCP-1, PAI-1, and angiotensinogen
- ↑ ceramides = ↑ adipose tissue inflammation and dysfunction that underlies cardiometabolic disease
  - Ceramides = signaling molecules derived from fat and protein metabolism that modulate adipocyte function to regulate glucose and lipid metabolism
- Can decrease production of other beneficial substances ie., adiponectin
- Leads to progression of IR

Park YM, et al. Adipose tissue inflammation and metabolic dysfunction: role of exercise. Mo Med. 2014;111(1):65-72.
Chaurasia B, et al. Adipocyte ceramiedes – the nexus of inflammation and metabolic disease. Front Immunol. 2020;11:576347.

How Do We Effectively Help Manage a Patient and Their Weight Loss Goals?

A Systems Biology Approach

Let’s Start at the Beginning

Factors to Focus On

- Cortisol / Stress
- Thyroid Issues
- Blood Sugar/Insulin
- Metaflammation
- Mitochondrial damage
- IR/Glucose regulation issues
- GUT-IMMUNE-BRAIN axis issues
- Toxin load/Detoxification Support
- Sex hormone balance
- Exercise and activity level
- Dietary changes

Metabolic Signaling

- Disruptors of metabolic signaling lead to:
  - Increased insulin resistance
  - Changes in neurochemistry
  - Fluctuations in primary hormones
- Abnormal metabolism results in weight gain, food cravings, fatigue and physiologic stress
- Glucose/insulin dysregulation
- Poor overall performance and metabolism

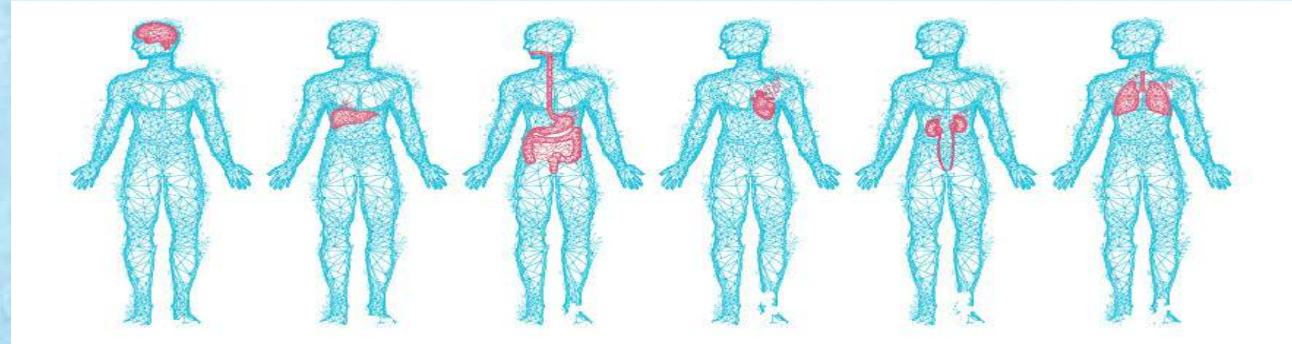
Metabolic Signaling Disruptors

- DIETARY choices
- Obesity
- Lack of exercise
- Sleep issues
- Chronic stress
- GUT/microbiome/LPS
- Infections
- Dental issues - periodontitis/gingivitis
- Metaflammation
- Increased oxidative stress
- Liver/Kidney/Lymph issues – detoxification
  - Drugs
  - Metals
  - Pesticides/POPs
  - Chemicals – sweeteners, dyes, preservatives, etc.

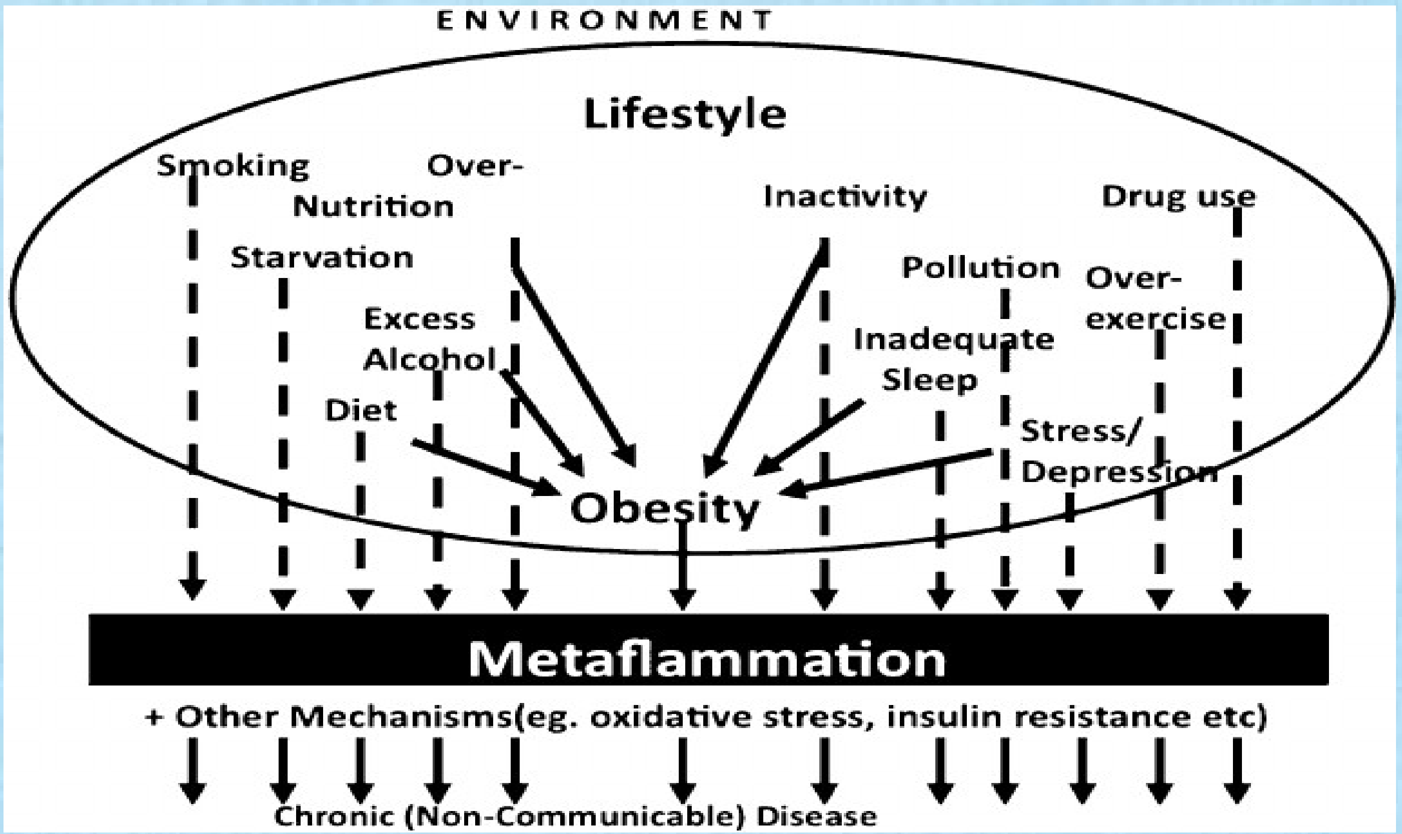
"Healthy Aging"

- Takes a systems biology approach to treatments
- Tones functional interconnectivity of organ systems

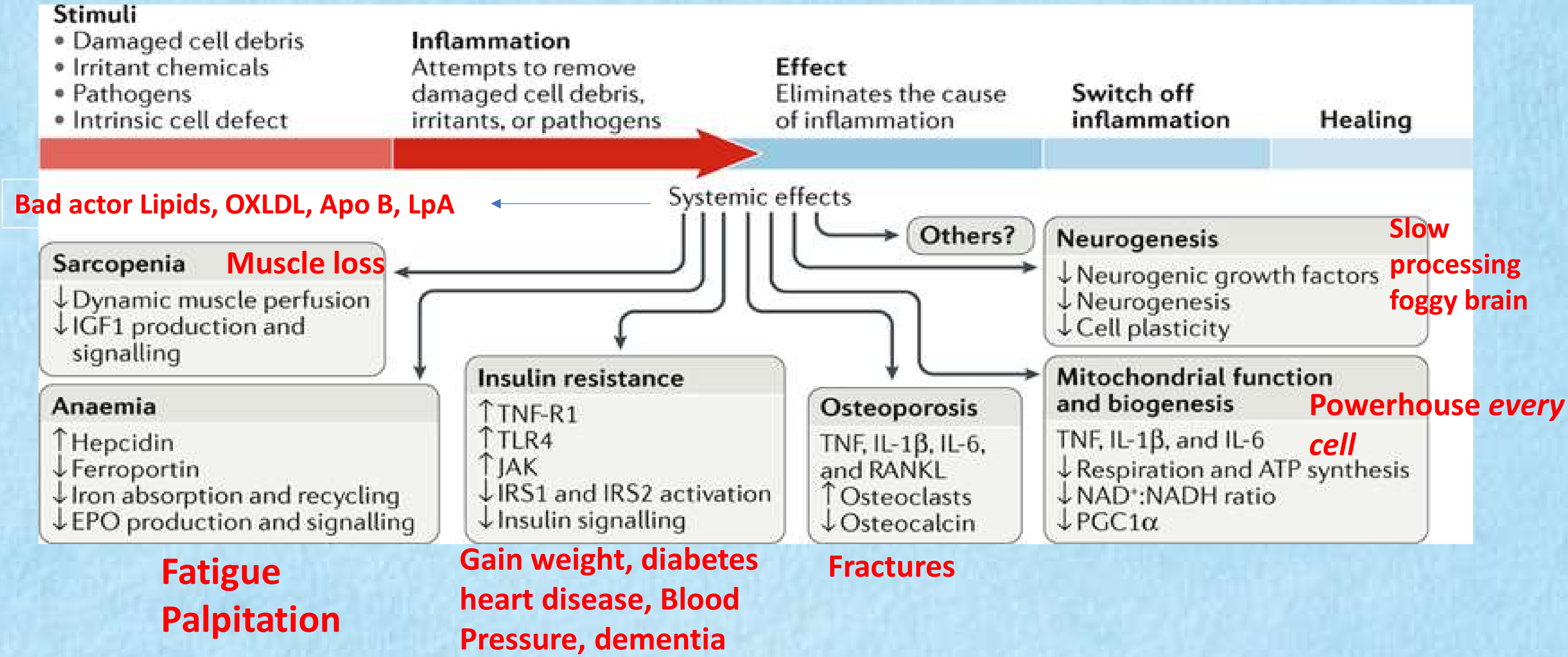
KEY = controlling **Metaflammation**



Metaflammation Constructs



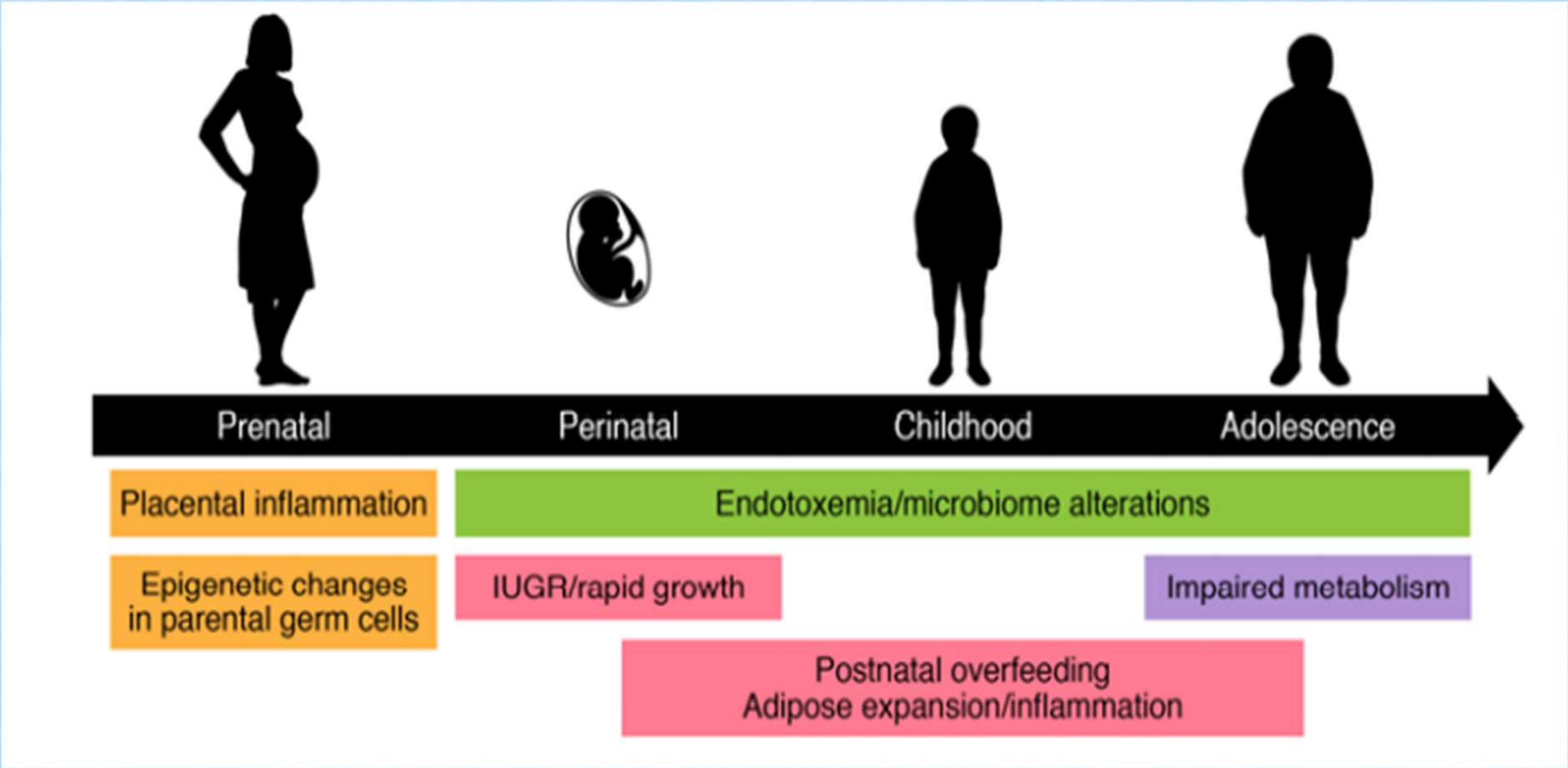
Egger G, et al. Obesity Reviews. 2008;10(2):237-49.



Metaflammation Leads to Inflammaging

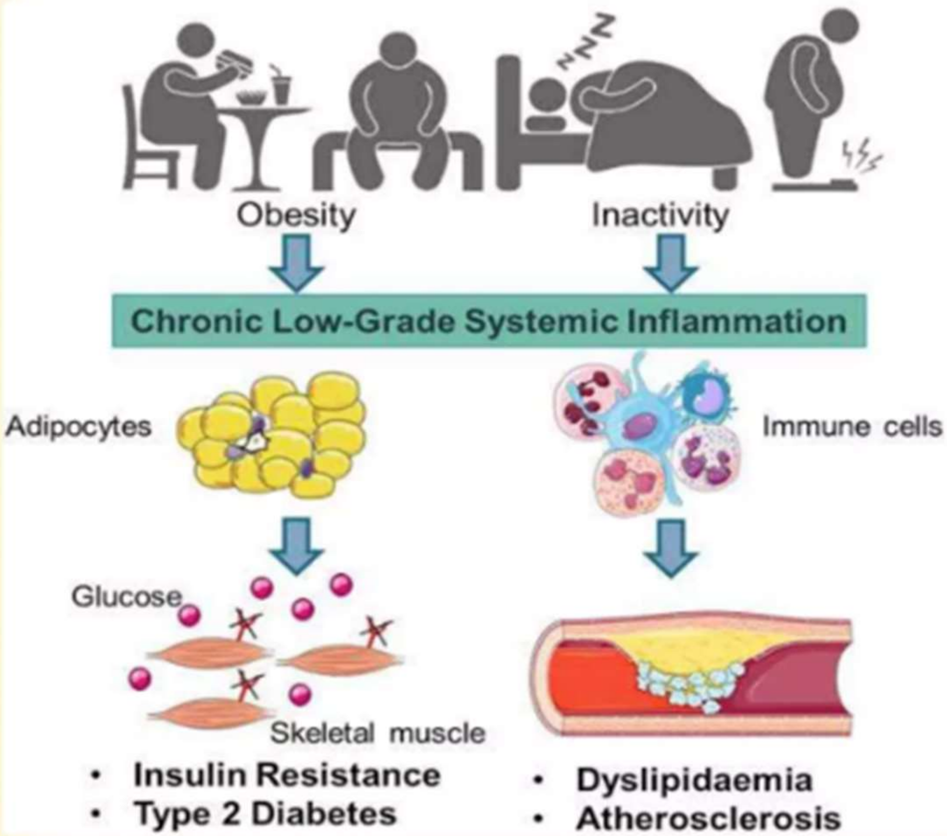
Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Metaflammation Constructs Begin in the Womb and Can Follow the Individual Through Life - Unless the Cycle is Broken



Kanakadurga S, et al. The initiation of metabolic inflammation in childhood obesity. J Clin Investig 2017;127(1):65-73.

Complications of Metaflammation =Weight Gain



Roche, H. (2019). Dietary modulation of energy homoeostasis and metabolic-inflammation. *Proceedings of the Nutrition Society, 78*(3), 313-318. doi:10.1017/S0029665118002872

Weight Gain and Inflammation

- Chronic inflammation = increased circulating cytokines level and C-reactive protein (CRP)
- Adipokine production driven by increased adipocytes and adipose tissue infiltration with inflammatory cells
- Reduction of body fat following both controlled diets or gastric surgery help reduce pro-inflammatory cytokines

Bianchi VE. Weight loss is a critical factor to reduce inflammation. Clin Nutr ESPEN. 2018;28:21-35.

Metaflammation and Obesity

- Altered homeostasis of nutritionally overloaded cells in obesity
- Elevated expression of pro-inflammatory cytokines from M1 macrophages in white adipose tissue – TNF alpha, IL-6, CRP, IL-1b etc…
- Decrease in anti-inflammatory cytokines from M2 macrophages – IL-10, IL-Ra, adiponectin, etc..
- Macrophage-like Kupffer cells increase pro-inflammatory cytokines
  - In response to transducer signals produced by white adipose
  - Leads to necroinflammation
  - "Cycle" of inflammation leading to tissue and cell death

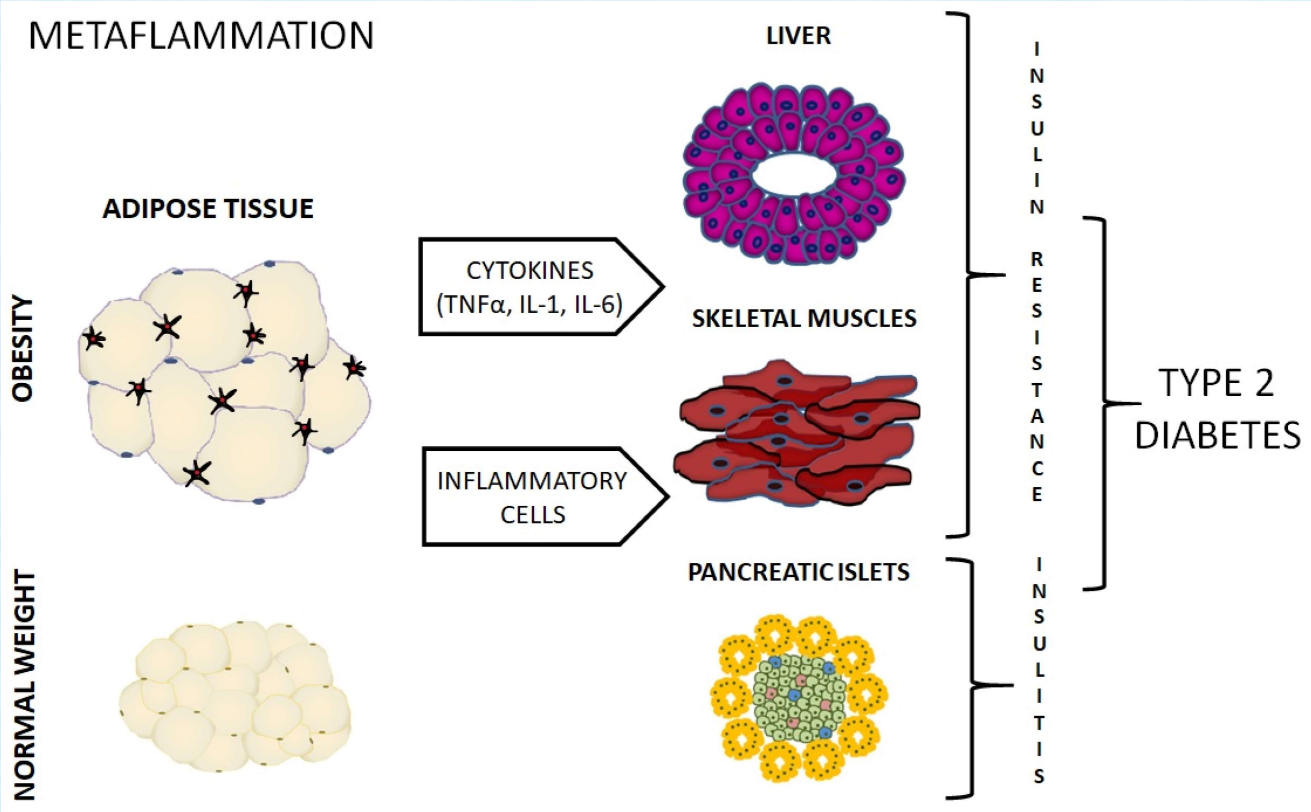
Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.

Metaflammation and Obesity

- Adipose tissue over-expression of chemoattractant CCL2 leads to macrophage infiltration, IR and hepatosteatosis
- Adipocytes under stress activate mTOR pathway
- Downregulation of AMP-activated protein kinase (AMPK) and SIRT pathways
- Muscle fibers suffer from decreased glycogen synthesis
- HPA axis dysregulation
- Insulin signaling issues

- Debnath M, et al. Obesity induced metaflammation: pathophysiology and mitigation. J Cytokine Biol. 2016;1:1.
- Li et. . Suppression of the mTORC1/STAT3/Notch1 pathway by activated AMPK prevents hepatic insulin resistance induced by excess amino acids. Am. J. Physiol. Endocrinol. Metab. 2014;306:E197–E209. (2014)

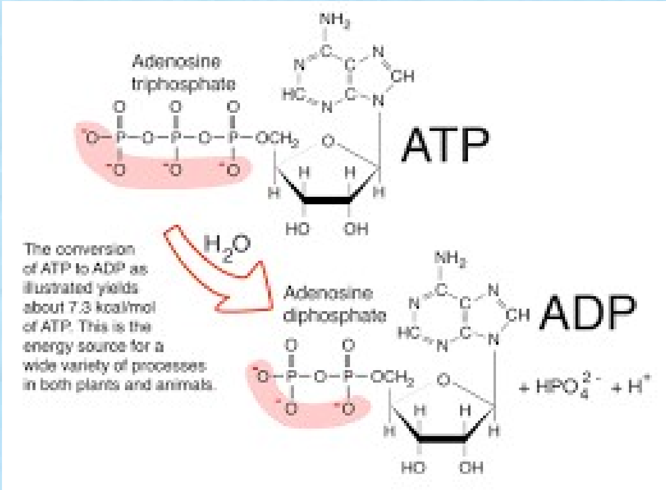
Metaflammation and T2D/ IR/Obesity



Kurylowicz A, et al. Molecules.2020;25(9):2224.

Mitochondria and Metaflammation

- Mitochondria Primary source of ATP
- Mitochondrial alterations play central role in aging process
- Altered mitochondrial function is linked to several acute and chronic inflammatory diseases
- Mitochondria major source of ROS
- Also targets and quenches ROS



Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory responise. Mitochondrion. 2013;13(2):106-118.

Mitochondria and Metaflammation

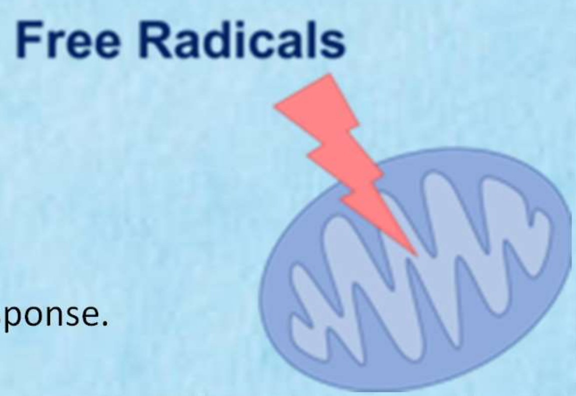
- Increased pro-inflammatory mediators alter mitochondrial function

- Increases mitochondrial oxidative stress = dysfunction

- Uncontrolled generation of ROS overwhelms cellular antioxidant protection of mitochondria

- Vicious cycle of inflammation

- increased IR, increased weight gain, increased aging



Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

Mitochondria and Metaflammation

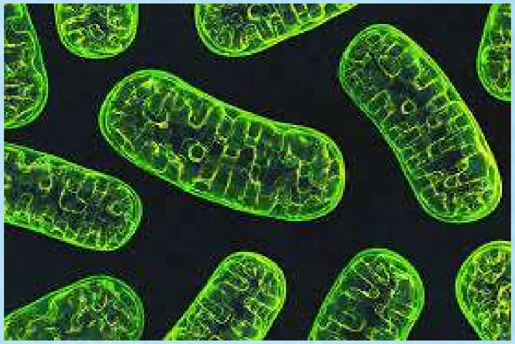
- Damage-associated molecular patterns derived from mitochondria contributes to inflammasome formation

- Also caspase-1 activation

- Alterations in mitochondrial autophagy may also lead to inflammation

Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

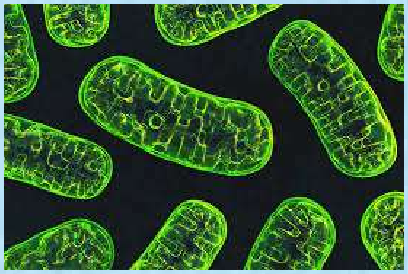
Mitochondrial Dysfunction



- Mitochondrial dysfunction activates the redox-sensitive factor NF-κB pathway
- Induces NLRP3 inflammasome activation
- NLRP3 inflammasome/NF-kB pathways work together to activate inflammatory cytokines
- Inflammatory mediators induce mitochondrial dysfunction.

Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

Mitochondrial Dysfunction and Obesity



- Nutrient excess leads to mitochondrial dysfunction
- Increased ROS and oxidative stress
- Consequential effects on lipid and glucose metabolism
- In turn leads to obesity related pathologies
- Mitochondrial oxidative dysfunction correlates with insulin resistance in skeletal muscle of obese and diabetic individuals
  - Correlates with reductions in mitochondrial numbers and size and enzymatic oxidative capacity
  - Reduced expression of OXPHOS genes and reduced oxygen consumption also observed in obese individuals

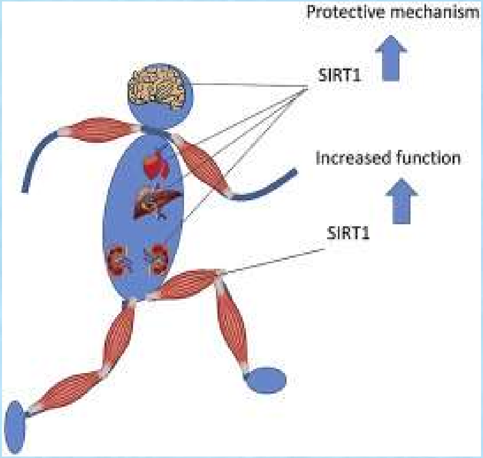
Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

Mitochondrial Dysfunction and Obesity

- Adipocytes help to maintain the appropriate balance between energy storage and expenditure
  - Maintaining this balance requires “normal” mitochondrial function
- Mitochondrial biogenesis and activity increase dramatically during adipocyte differentiation
- Mitochondrial dysfunction in mature adipocytes linked to defects in :
  - Fatty acid oxidation
  - Secretion of adipokines
  - Dysregulation of glucose homeostasis
- Reduction in oxidative capacity of brown adipocytes results in impaired thermogenesis
  - Linked to diet-induced obesity

Lopez-Armada MJ, et al. Mitochondrial dysfunction and the inflammatory response. Mitochondrion. 2013;13(2):106-118.

Mitochondria & Sirtuins



- Cellular demands during exercise results in

adaptive responses signaling proteins

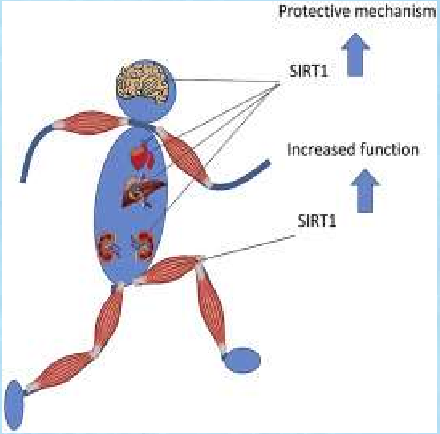
- SIRT1 – SIRT7
- SIRT1 – NAD+ dependent lysine deacetylase located

intracellularly in nucleus

- SIRT 1 activates biogenesis and mitochondrial oxidative capacity via PGC1alpha
- Regular exercise reported to improve SIRT1 levels in kidney, liver, brain in neurodegenerative disease patients
- In skeletal muscle, over-expression of SIRT1 results in enhanced numbers of myonuclei
    - improves the repair process after injury
    - Actively involved in muscle hypertrophy by up-regulating anabolic and downregulating catabolic processes

Radak Z, et al. The systemic role of SIRT1 in exercise mediated adaption. Redox Biology. 2020;35:101467.

Mitochondria & Sirtuins



- SIRT3 located in mitochondria
- Together with SIRT1 - jointly activates ATP

production and mitochondrial antioxidant function

- SIRT3 more expressed in type I muscle fiber
- SIRT3 dynamically responds to exercise to potentially impact muscular energy homeostasis via AMPK and PGC-1α

- Note Thai ginseng (*Kaempferia parviflora*) 5,7 dimethoxyflavone is the most potent SIRT1 upregulating plant known
- 4-5 x resveratrol SIRT1 activity

Radak Z, et al. The systemic role of SIRT1 in exercise mediated adaption. Redox Biology. 2020;35:101467.
Nakata A, et al. Potent SIRT1 enzyme-stimulating and anti-glycation activities of polymethoxyflavonoids from Kaempferia parviflora. Nat Prod Commun. 2014;9(9):1291-4.

Mitochondria and Skeletal Muscle

- Plays role in muscle :
  - Cell metabolism
  - Energy supply
  - Regulation of energy-sensitive signaling pathways
  - Regulation of ROS (reactive oxygen species) generation/signaling
  - Calcium homeostasis
  - Muscle cellular apoptosis
- Skeletal muscle mitochondrial oxidative capacity declines with age
- Negatively affects walking performance

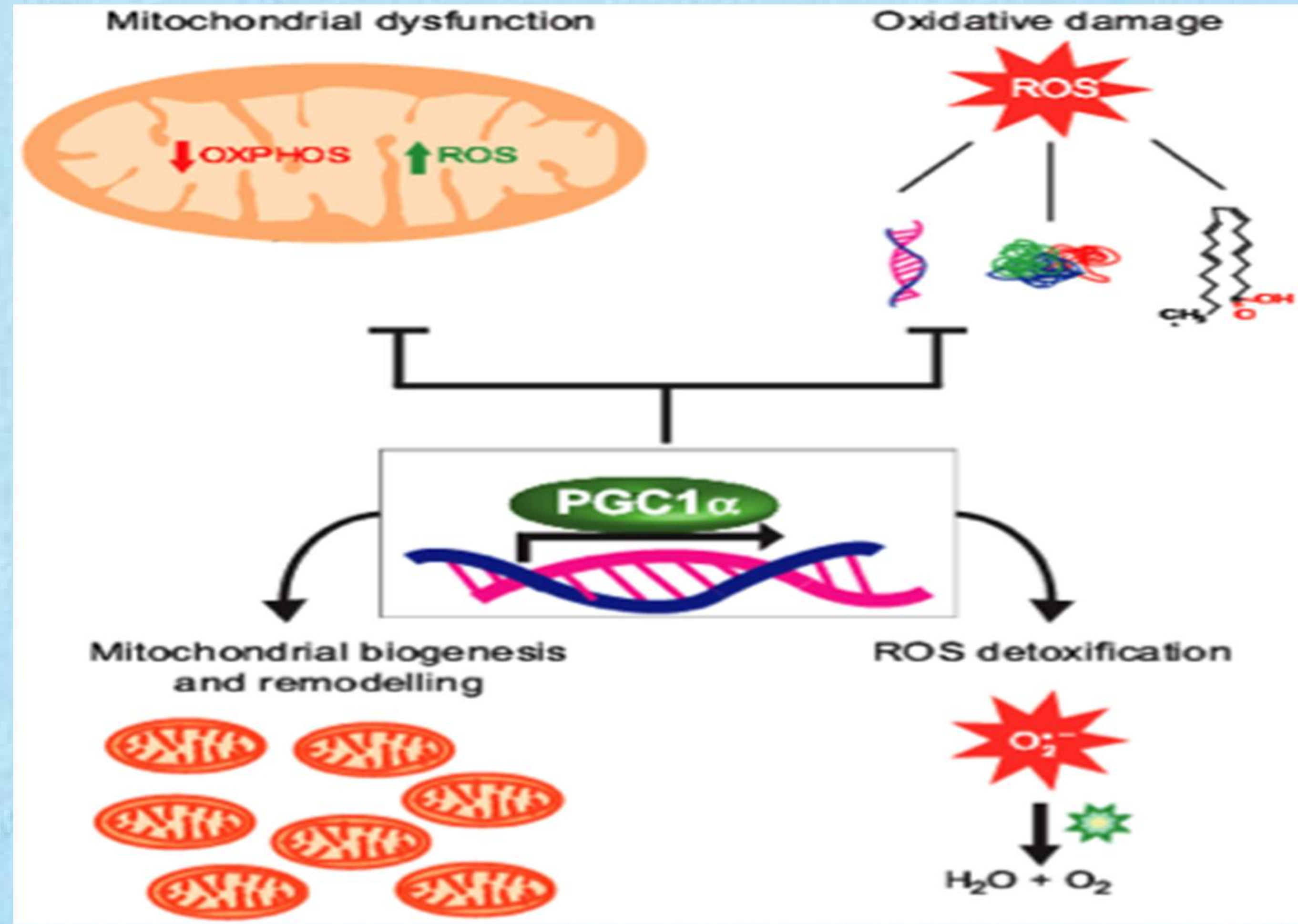
Carter HN, et al. Mitochondria, muscle health, and exercise with advancing age. Physiology. 2015:30(3):208-223.

Mitochondria and Skeletal Muscle

- Improved mitochondrial function associated with improved performance

- Skeletal Muscle Mitochondrial dysfunction associated with:
  - Increased insulin resistance
  - Loss of muscular strength
  - Loss of muscle mass
  - Atrophy

Carter HN, et al. Mitochondria, muscle health and exercise with advancing age. Am Phys J. 2015;30(3):208-223.


Mitochondrial dysfunction
Oxidative damage
OXPHOS
ROS
ROS
PGC1α
Mitochondrial biogenesis
and remodelling
ROS detoxification
H2O + O2

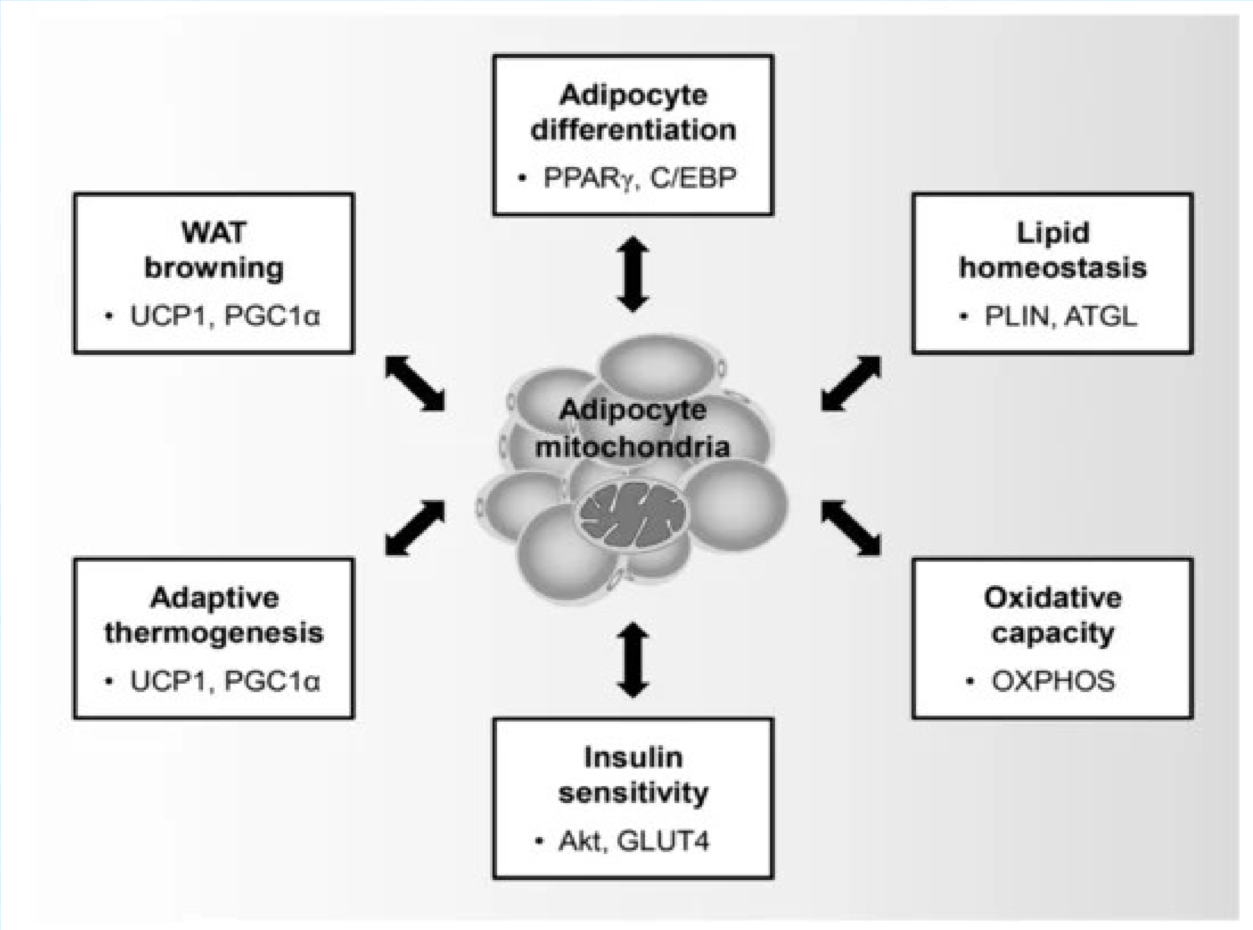
Adipocyte Mitochondria

Regulate:

- Adipocyte differentiation
- Lipid homeostasis
- Oxidative capacity
- Insulin sensitivity
- Adaptive thermogenesis
- Browning of white adipose tissues

Lee JH, et al. Int J Mol Sci. 2019;20(19):4924.

Adipocyte Mitochondria

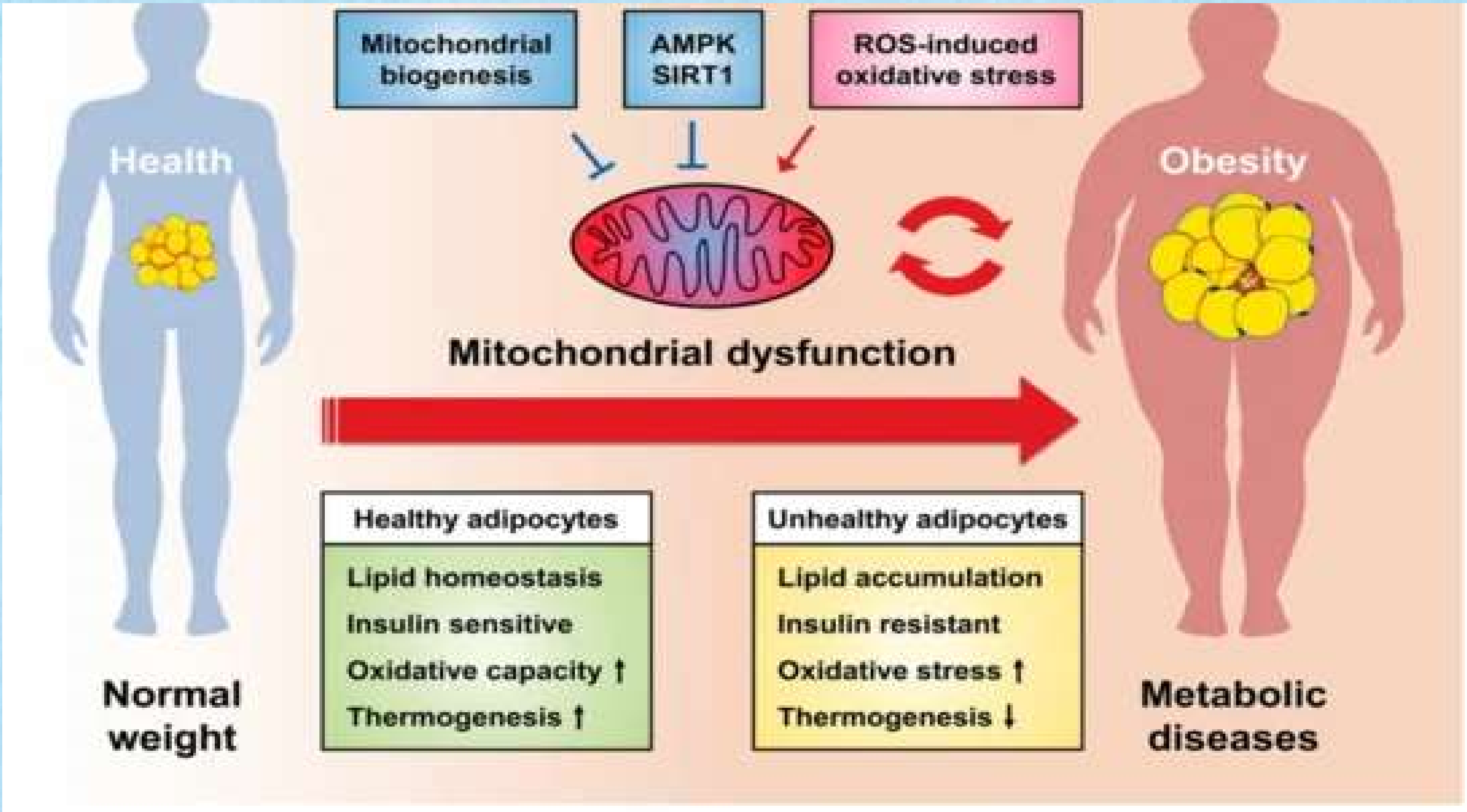


Lee JH, et al. Int J Mol Sci. 2019;20(19):4924.

Mitochondrial Dysfunction in Adipocytes

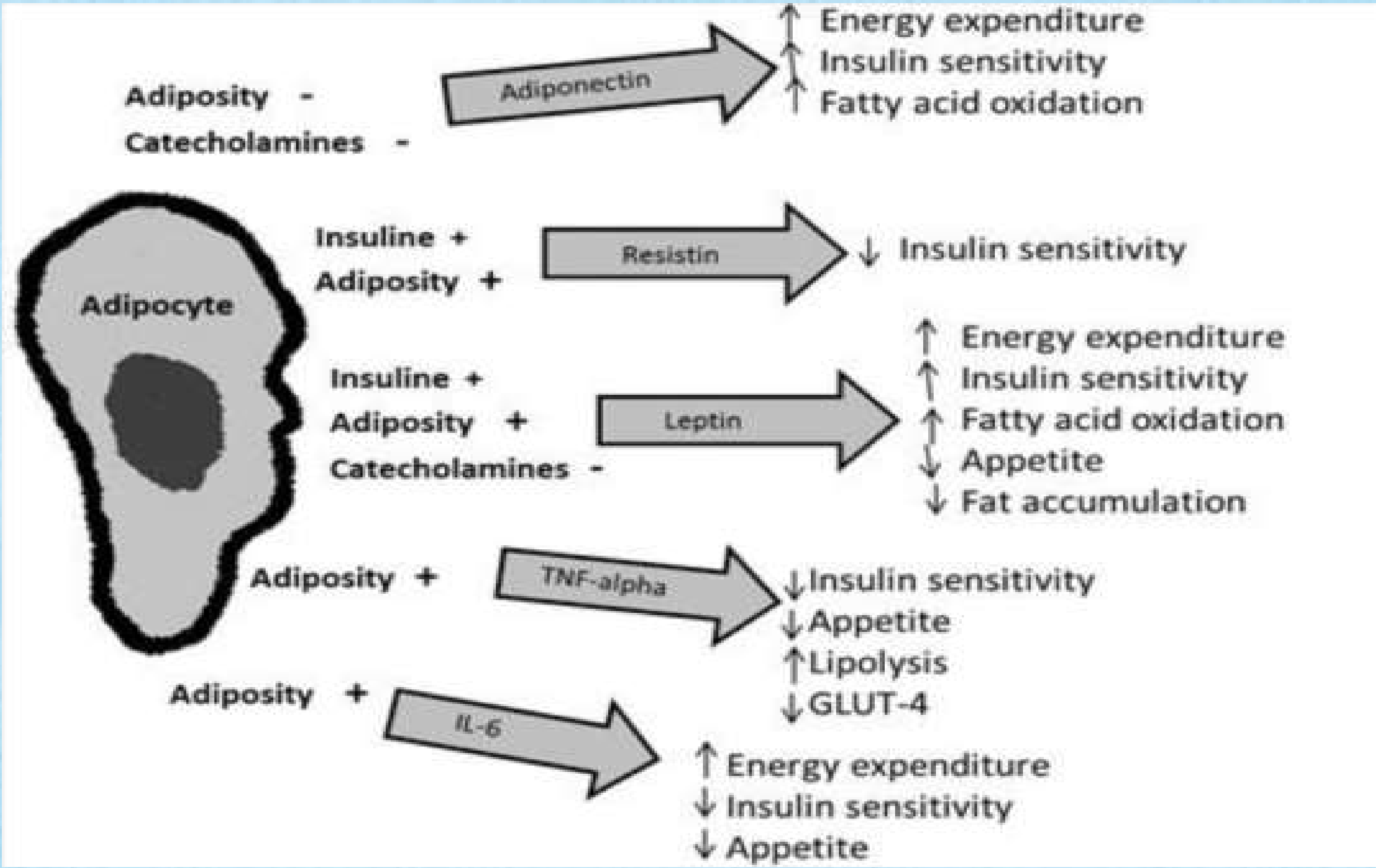
- Increased ROS production
- Alteration of mitochondrial genome
  - Reduction of mitochondrial mass due to decreased mitochondrial biogenesis
  - Mutation of DNA
- Dysregulated mitochondrial dynamics
- Altered mitophagy and mitochondrial turnover

Lee JH, et al. Int J Mol Sci. 2019;20(19):4924.



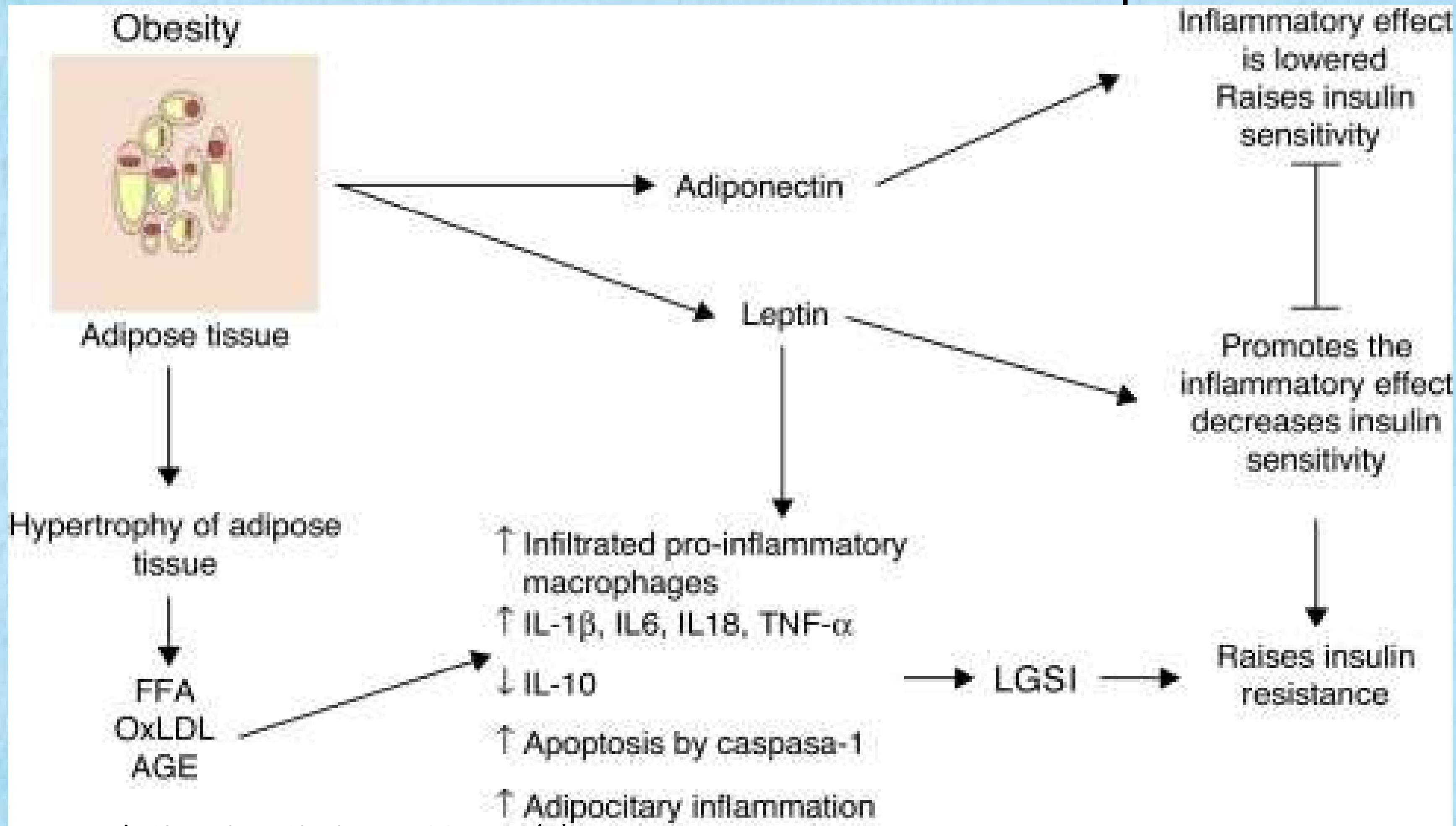
Lee JH, et al. Int J Mol Sci. 2019;20(19):4924.

Major Adipokines and Their Role



Fernandez-Sanchez A, et al. Int J Mol Sci. 2011;12(5):3117-32.

Metaflammation of Visceral Adipose Tissue



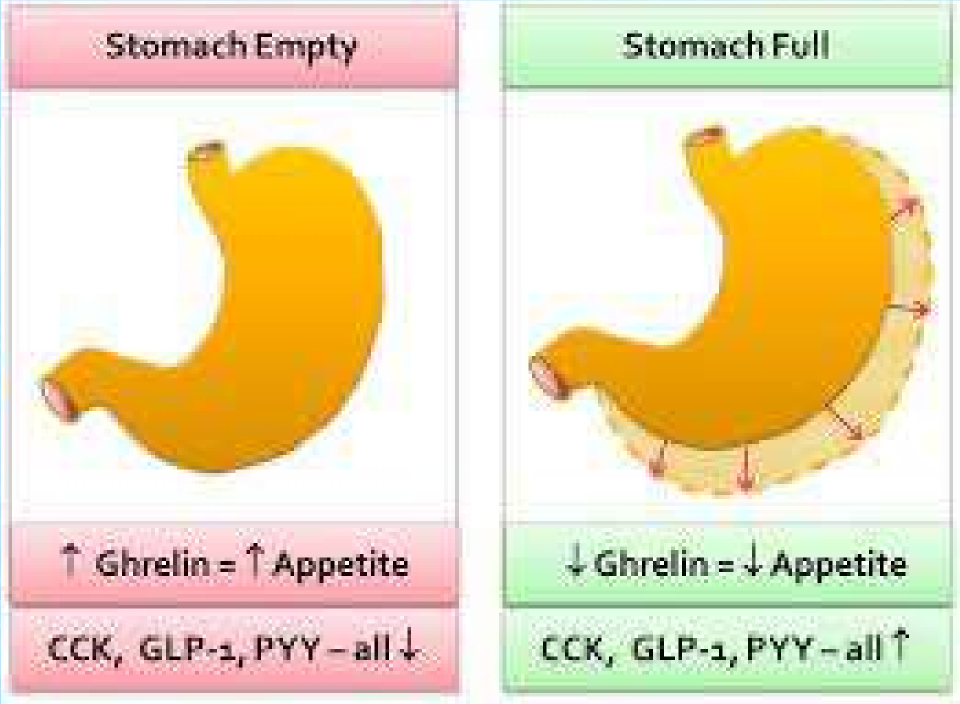
Leon-Pedroza JI, et al. Cirguria y Cirujanos. 2015;83(6):543-551.

Ghrelin

- Produced in enteroendocrine cells

of GUT

- Hunger hormone
- Increases drive to eat
- Blood levels highest before meals when hungry
- Return to lower levels post mealtimes



Adiponectin

- Increases insulin receptor sensitivity
- Elevates AMP kinase which ↑ glucose transport into skeletal muscle and burning of fat (fatty acid oxidation)
- Current top target for glucose control along with incretins (GIP, GLP-1).
- Anti-athrogenic properties
- IL-6, TNFα inhibit adiponectin release

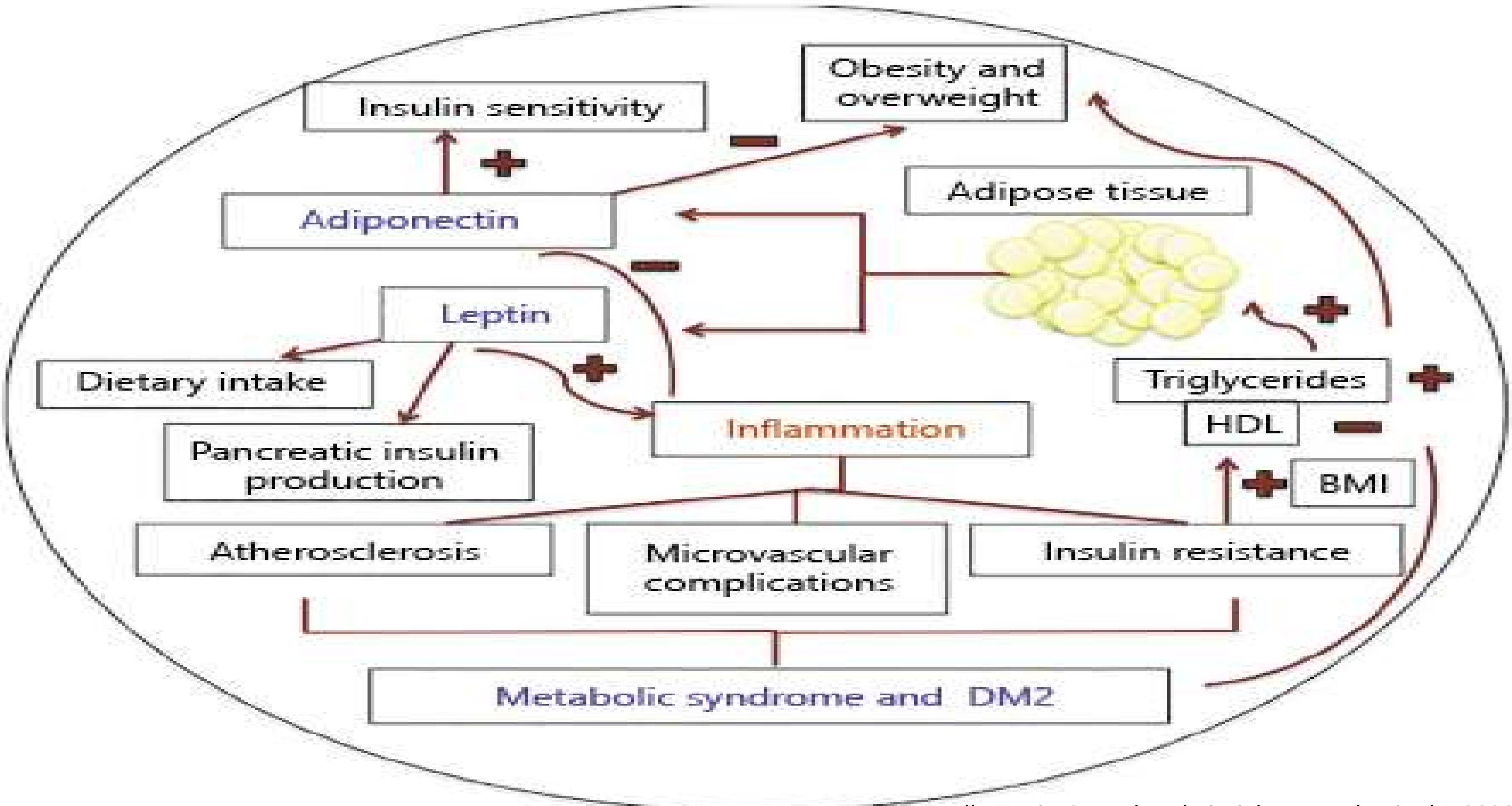
Frühbeck G, et al. Adiponectin-leptin ratio is a functional biomarker of adipose tissue inflammation. Nutrients. 2019;11(2):454.

Leptin

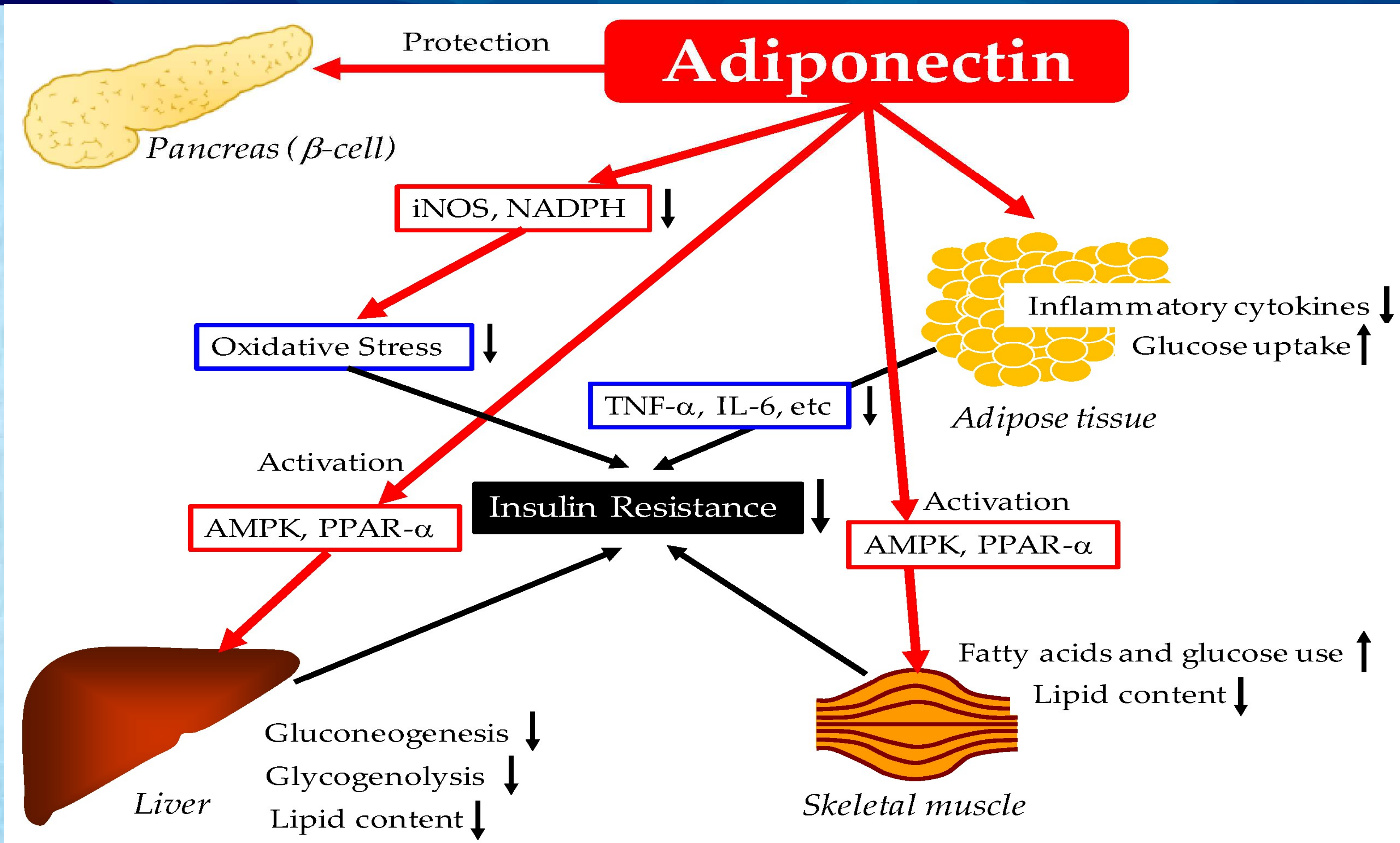
- Reduces intracellular lipid levels in skeletal muscle, liver and beta cells, improves insulin receptor fx
- Genetic component for leptin receptor mutations (morbidly obese, hyperphagic, decrease sexual maturation)
- Leptin resistance & elevations lead to arterial thrombosis (platelet leptin receptor)
- Informs body of fat stores signal for satiety

Frühbeck G, et al. Adiponectin-leptin ratio is a functional biomarker of adipose tissue inflammation. Nutrients. 2019;11(2):454.

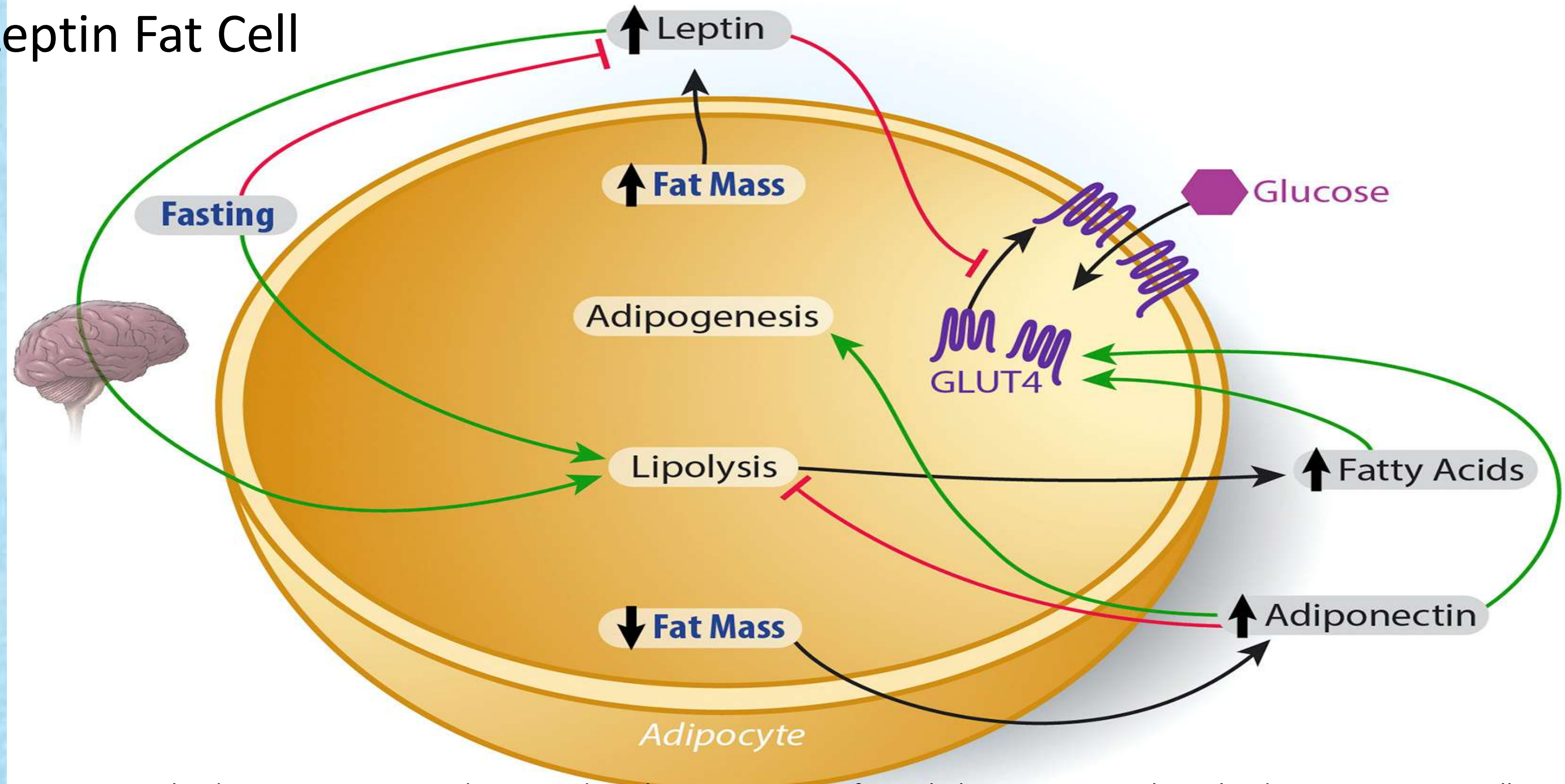
Adiponectin / Leptin and Obesity



Albarracin G, et al. Dubai Diabetes Endocrinol J. 2020;26:93-102.


Adiponectin
Protection
Pancreas (β-cell)
iNOS, NADPH
Oxidative Stress
TNF-α, IL-6, etc
Inflammatory cytokines
Glucose uptake
Adipose tissue
Activation
AMPK, PPAR-α
Insulin Resistance
Activation
AMPK, PPAR-α
Fatty acids and glucose use
Lipid content
Gluconeogenesis
Glycogenolysis
Lipid content
Liver
Skeletal muscle

Leptin Fat Cell



Stern JH, et al. Adiponectin, Leptin, and Fatty Acids in the Maintenance of Metabolic Homeostasis through Adipose Tissue Crosstalk. Cell Metab. 2016;23(5):P770-84.

Adiponectin and Mitochondria

- Adiponectin is an anti-diabetic adipokine
- Mitochondrial function linked to adiponectin synthesis in adipocytes
- Mitochondrial dysfunction increased with excess adipose tissue
- Decreases plasma adiponectin levels

Koo EH, et al. Essential role of mitochondrial function in adiponectin synthesis in adipocytes. Diabetes. 2007;56(12)L2973-81.

Adiponectin and Mitochondria

- Adiponectin induces Ca^{++} influx via receptor
- AdipoR1 = adiponectin receptor
- Suppression of AdipoR1 results in decreased PGC-1α
- **Leads to decreased mitochondrial content**
- **Decreased blood glucose control**

Wang Y, et al. Plasma adiponectin levels and type 2 diabetes risk: a nested case-control study in a Chinese population and an updated meta-analysis. Sci Reports. 2018;8(1):406.

Weight Loss Systems Biology Management

- Target:
  - *Stress/cortisol
  - *IR
  - *GUT-Immune-Brain
  - Optimize sex hormones

- *Discussed today in upcoming presentations

Weight Loss – Precision LABs

- BMI
- CMP
- CBC with Diff
- FBS/Insulin/A1C
- Cortisol serum
- CRP-hs
- RBC Mag
- Neutrophil/lymphocyte ratio
- Vitamin D total
- TSH, T3F, T4F, TPO, ThyroGlob
- Homocysteine
- B12/RBC folate, Zinc
- Lipase/Amylase
- Fibrinogen
- Iron, total
- TIBC
- % Saturation
- Ferritin
- *VEGF
- *TGF-beta1
- *MMP-9
- Advanced Lipid panel
- *Gal-3
- *Adiponectin/Leptin
- *4 point salivary cortisol

*** Optional**


THANK YOU!


ANY QUESTIONS ?