ENDOGENOUS INFLAM-AGING

mTOR and Senescent Cells

Anti-INFLAM-AGING Strategies = LIVE STRONGER LONGER

AGING is not a disease. It is a natural part of life. However, as that normal process runs its natural course, there is much you can do to minimize its less desirable consequences. And, there is so very much you can do with a Nutri-Spec individualized, life-long nutrition plan --- for yourself, for your family, and for your patients --- so you will all ---

LIVE STRONGER LONGER.

With Nutri-Spec you can target specifically the underlying forces that drive the aging process. With Nutri-Spec you do not focus on the consequences of the aging process --- you target the causative factors --- the foundational ---

Immuno-Neuro-Endocrine Stresses ---

INE Stresses that accelerate the changes of aging ---

AT THE CELLULAR LEVEL.

NUTRI-SPEC --- with your…

- ACTIVATOR + REJUVENATOR
- ADAPTO-MAX + OXY-MAX
- IMMUNO SYNBIOTIC
- OXY TONIC +/- ELECTRO TONIC +/- OXY D+ of your BALANCING PROCEDURE.

--- elevates your clinical power to a level you never dreamed possible.

Contemplate this …

EXOGENOUS AGING

Everyone "knows" about it (but is lost in contradictions).

Determines Health Span.

Intrudes upon cells "from the out-side in".

Driven By Oxidative Stress:

- unhealthy Microbiota
- nutrient insufficiency
- high fructose diet
- high HOHUM-PUFA
- sleep disturbance
- emotional stress
- radiation exposure
- UV & blue-green light
- mold, & other toxins
- ENDOGENOUS AGING

Aging begins (theoretically) at the moment of conception.

Catabolic Processes

Benefitted By:

- Immuno-Synbiotic
- Activator
- Adapto-Max
- Oxy-Max
- BALANCING PROCEDURE

ENDOGENOUS AGING

Only Gerontologists (& now you) know about it.

Determines Lifespan.

Alters cell function "from the inside-out".

By Genetic Metabolic Clock:

- unhealthy Microbiota
- Senescent Cell formation
- SASP
- mTOR
- deficient autophagy
- dysregulated apoptosis
- EXOGENOUS AGING

Aging begins on the 23rd birthday.

Anabolic Processes

Benefitted By:

- Immuno-Synbiotic
- Activator
- Adapto-Max
- Rejuvenator
- BALANCING PROCEDURE

Yes, there are 2 parallel and, believe it or not, mostly autonomous aging metabolic pathways. We of NUTRI-SPEC label these "EXOGENOUS Aging" & "ENDOGENOUS Aging".

Beginning at age 23, ENDOGENOUS Aging rapidly supplants EXOGENOUS Aging as the major force driving INFLAM-AGING.

mTOR (mammalian Target of Rapamycin) is strongly implicated in the aging process, and it is also found that reduced mTOR signaling promotes longevity.

The two types of mTOR (mTORC1 & mTORC2) coordinate Anabolic and Catabolic metabolism at the cellular level. But, mTOR signaling is essential for metabolic regulation at the organismal level as well. Proper mTOR signaling in response to changing environmental conditions is crucial.

KEY CONCEPT: mTORC1 & mTORC2 drive anabolic metabolic processes. From birth to a human being's complete maturity (at age 23) mTOR is essential to development.

But at maturity, mTORC1 turns abruptly from friend to foe.

At maturity, mTORC1 continues to push anabolic metabolism --- which is now totally inappropriate. ENDOGENOUS Aging as non-physiological anabolism becomes ever more dominant in driving Immuno-Neuro-Endocrine Stress.

Why do humans continue to exhibit non-productive (and ultimately damaging) anabolism from maturity through old age? The objective of biological intelligence here is easily understood. The human species (like all mammals) has existed for many, many millennia in a natural environment where scarcity, hunger, and even starvation were common. Food deprivation led to catabolic stress, and the species needed a strong, easily activated anabolic drive to maintain tissue structure and function even in the face of extreme catabolism.

Contemporary affluent society now suffers precisely the opposite metabolic stress --- the availability of food in grotesquely abundant quantity, and qualitatively addictive content. ----- Yet --- the mTOR anabolic drive continues unabated. The consequences include pathological hyperplasia, pathological hypertrophy, and an oversaturation of many metabolic pathways.

As a person ages, we see the EXOGENOUS catabolic damage aspect of aging become of less significance than is the destructive influence of ENDOGENOUS

anabolism out of control --- as seen in INFLAM-AGING consequences that appear over a Lifespan.

As shown in an exhaustive study [Kulkarni, et al. Geroscience-guided repurposing of FDA-approved drugs to target aging: a proposed process and prioritization. Aging Cell.] there are just a few drugs and nutrients that show strong evidence for the extension of Lifespan and the reduction of mortality in humans. Gerontologists call them "REJUVENINS"

High on this list of gerotherapeutic Rejuvenins is Rapamycin, the drug Gerontologists have found to effectively block excess mTORC1 activity. As Gerontology steadily reveals the many anti-INFLAM-AGING mechanisms by which Rapamycin protects health in aging --- it is seen that other Rejuvenins often work by the same mechanism --- inhibiting mTORC1.

Also making the "TOP 10" list of Rejuvenins are 5 nutrients prominent in your NUTRI-SPEC supplements …

--- NAD (+) & its precursors (Nicotinamide Riboside & Nicotinamide Mononucleotide) = Found in ACTIVATOR.

--- Quercetin = The flavonoid found in ACTIVATOR, Oxygenic D, Complex P, and Formula EI.

--- N-Acetyl-Cysteine (NAC) = found in ACTIVATOR and REJUVENATOR

--- But, NAC acts as a Rejuvenin only to the extent it combines to form Glutathione intracellularly with Glycine = found in ACTIVATOR, REJUVENATOR, OXYGENIC G, and OXYGENIC K.

--- Carnosine = found in REJUVENATOR, ADAPTO-MAX, OXYGENIC D.

The only other intervention shown to extend Lifespan, not only in humans but in a wide range of organisms, is caloric restriction --- defined as a reduction in nutrient intake without malnutrition. Given the critical role of mTORC1 in sensing nutrients and insulin, many speculate that the beneficial effects of caloric restriction on Lifespan are also due to reduced mTORC1 signaling.

In most aging-related changes, EXOGENOUS Oxidative Stress (OxS) appears to have a direct connection with INFLAM-AGING and cell senescence. OxS and INFLAM-AGING increase the aging-related phenotype and induce and aggravate the inflammatory response, creating a chronic state of systemic inflammation.

----- OxS very definitely contributes to the undesirable changes that progress as we age. But, these consequences of INFLAM-AGING relate to our Health Span --- yet do not correlate with Lifespan.

Does this mean there is no connection between OxS and aging? No, it does not. The intracellular portion of the damage from OxS directly feeds into the largely pre-programmed processes of Endogenous Aging (= INFLAM-AGING 'from the inside-out").

Via Exogenous OxS ("from the outside-in"), that Endogenous process of INFLAM-AGING is magnified --- with the production of additional inflammation --- that then feeds right back into the Exogenous process of INFLAM-AGING --- in a vicious cycle.

Picture it this way … Exogenous Aging (which is a major determinant of Health Span) is driven by external forces --- the environmental stresses that elicit OxS:

- unhealthy microbiota
- mold & other toxic exposure
- radiation exposure
- excess UV light exposure
- excess blue-green light exposure + deficient red-yellow (sun)light
- emotional stress,
- sleep disturbance,
- nutrient deficiency,
- high sugar diet,
- high vegetable oil diet.

But there is one other factor that exacerbates Exogenous Aging --- one that derives from the inside out --- from one aspect of Endogenous Aging. That factor, mitochondrial-associated functional and structural damage, is at the core of both Endogenous Aging and Exogenous Aging.

------- Senescent Cells produce their own Endogenous INFLAM-AGING, independent of OxS-generated Exogenous INFLAM-AGING --- but exacerbated by it. A vicious cycle emerges --- with Exogenous INFLAM-AGING shortening Health Span --- while provoking increased Senescent Cell Endogenous INFLAM-AGING attack on Lifespan.

The exogenous OxS inflammation feeds even more endogenous generation of inflammatory cytokines (--- NF-kB, TGF-β) back into the already suffering Lifespan --- which then flows back into ever more exogenous OxS inflammation, and its damage to Health Span.

This Immuno-Neuro-Endocrine Stress associated with chronic inflammation and leading to INFLAM-AGING is found in cell/tissue processes even in

younger individuals. Diabetic patients (both T2D and T1D), by several mechanisms, including particularly elevated Advanced Glycation End products, are particularly susceptible to these premature processes of INFLAM-AGING.

Although the Free Radical Theory of Aging (--- what we now more appropriately term Exogenous INFLAM-AGING) has been well-acknowledged for many decades, conflicting evidence is piling up in research throughout the 21st century. This more recent evidence not only seems to disprove the entire theory of Oxidative Stress (OxS) as the primary cause of aging, but goes on to show that attempting to control OxS with antioxidants is not only futile --- but actually damaging in many cases.

----- The uncomfortable truth? --- Injudicious supplementing with antioxidants can make us die young. ----- Ouch.

As paradoxical as it may seem --- Oxs-generated ROS (Reactive Oxygen Species) --- as long as they are not produced excessively, and as long as they are controlled --- serve a critical function as signaling molecules that induce protective defense in response to age-dependent damage.

----- The truth --- is enough to make everyone connected to the health food industry squirm a bit, since it invalidates the premise of half the Nature Cure Remedies they peddle. Yes, the truth is that not only do ROS not cause life-shortening damage, but actually protect us against aging.

The only argument for antioxidant supplementation derives from Harman's Free Radical Theory of Aging. Harman was the first to postulate that aging results from accumulation of ROS-mediated damage. The problem with that theory is that the amount of ROS-mediated damage required to shorten Lifespan is almost never achieved without major (and uncommon) traumatic or chronic exposure to exogenous toxins or to radiation.

------- Even Harman, the father of the ROS Theory, acknowledged in a 2003 interview that the notion of ROS being THE cause of aging was based on a "wild guess".

Thousands upon thousands of research studies have confirmed that oxidative damage can indeed be detrimental --- creating …

- pathophysiological inflammatory reactions in the immune system,
- catabolic tissue destruction,
- and organ dysfunction.

--- But, the whole truth? ----- The damage from Oxidative Stress (OxS) significantly decreases Health Span, but NOT Lifespan.

Health Span is shortened by all the environmental stresses that elicit OxS --- exogenously --- from the outside in --- the ROS generators listed on Page 5.

These environmental sources of ROS cause exogenously-derived pathophysiology (= from the outside in), and so we can say Health Span is shortened by Exogenous Aging.

Lifespan is shortened by entirely different, endogenously-derived, processes (= from the inside out). ----- In other words, we live and die with OxS, but not of it. ----- The length of life depends upon Endogenous Aging.

What you need --- for yourself, your family and your patients --- is an individualized, comprehensive, life-long nutrition plan --- your ----

"SOLID DNP".

Your Stage Of Life INFLAM-AGING Defense Diphasic Nutrition Plan ...

Age 13 = Growth & Development --- Feed it!

Age 23 = Your Growth & Development Machine just turned into an aging machine.

Age 33 = You are "over the hill".

Age 43 = You are slipping down the hill.

Age 53 = You are tumbling down the hill.

If you read the short explanation of your SOLID DNP, you will begin to see how and why supplementation needs to be changed as all individuals go through their various stages of life. You will particularly see where REJUVENATOR fits into the picture.

STAGE OF LIFE INFLAM-AGING DEFENSE

Based largely on the function of mTORC1, we can propose a Stage of Life Plan to maximize mTORC1 inhibition, while minimizing Senescent Cell development.

Humans are not fully developed physically, mentally, and emotionally until age 23. The Developmental Stage of Life needs mTORC1 to maximize development.

At age 23, mTORC1 suddenly becomes a liability rather than an asset. As explained above, mTORC1 continues to promote anabolic functions that are completely inappropriate --- and ultimately damaging --- in the fully developed human. So, at age 23 the goal becomes minimizing the effects of mTORC1.

----- While the reasonably high-protein diet up until age 23 supports quality development, a lower protein diet --- and particularly a diet low in leucine, methionine and arginine, protects against the trend to senescence that begins at age 23.

We can postulate that between age 23 and 33 there may be a period when excessive physical, mental, and emotional demands on an individual can place a demand for continuing a reasonably high-protein intake --- and for mTORC1 --- though not as high as was needed before age 23. That reasoning applies particularly to those who are in athletic training. (This is not an endorsement of a "high-protein diet", but rather just a comment that protein intake need not be as severely restricted as it will be beginning at age 33).

----- Supplementation with Activator and Immuno-Synbiotic is essential --- along with the ideal combination of Oxy Tonic, Electro Tonic, and/or Oxy D+ as determined by THE BALANCING PROCEDURE. Rejuvenator is required only by individuals in comparatively poor health, or under extreme environmental stress.

At age 33, the metabolic shift towards senescence is maximized. mTORC1 must be inhibited, and senescent cells must be blocked at all costs. At this point, the lower protein diet is critical --- as is the need for at least a 12-hour fast every day. From age 33 through 52, protein intake will beneficially average around 10% of caloric intake. (= 200-300 calories = 50-75 grams = 7-11 ounces of meat/fish/poultry/eggs/cheese daily.)

----- Supplementation must include --- in addition to Activator and Immuno-Synbiotic --- Rejuvenator, and Oxy Tonic, Electro Tonic, and Oxy D+ as per the BALANCING PROCEDURE. ----- There is at age 33, a critical need for the Stage Of Life INFLAM-AGING Defense Diphasic Nutrition Plan (SOLID DNP).

At age 43, the SOLID DNP must be intensified. Endogenous Aging becomes Raging INFLAM-AGING. Rejuvenator must be the highest priority, and the anti-oxidant supplementation must be decreased.

At age 53, the metabolic needs take another turn. At this time, senescence begins to cause the breakdown of protective factors. While supplementation with Rejuvenator (Glycine + NAC + Lipoic Acid + Carnosine) was beneficial for those age 23-52 --- at age 53 such supplementation becomes critical --- but must be accompanied by a slight increase in dietary protein intake.

Metabolic Stages of Life:

- First week of life = Feed colostrum, then milk (6% protein, 40% sugar, 54% fat)

- Birth through 4 months = milk

- At age 4-6 months iron stores have been depleted (--- there is no iron in human milk) --- a daily serving of meat (1-2 ounces accompanied by non-starchy vegetables such as green beans, wax beans, zucchini or other summer squash) is required

- Age 4 months through development of dentition = 1 feeding daily to consist of meat and non-starchy vegetables --- other meals = milk

- With dentition, increasing amounts of more complex carbs, gradual weaning from human milk, and gradual increase of non-human milk, cheese, meat, fish, poultry and eggs

- Early childhood through age 23 = every meal must include at least a small portion of meat, fish, poultry, eggs or cheese, and carbohydrates up to the limit of adipose gain

- Age 23-32 food enters the mouth no more than 3 times daily; each feeding consists of a very small portion of meat, fish, poultry, eggs or cheese; carbohydrate to adipose limit; minimum 12-hour fast daily

- Age 33-52 no more than 3 feedings daily, each with a very small portion of meat, fish, poultry, eggs or cheese; carbohydrate to adipose tolerance; 12-hour fast every day; 5 hours between feedings

- Age 53+ the only change is a <u>slight</u> increase in meat, fish, poultry, eggs or cheese intake, with emphasis on a <u>minimum</u> 12-hour daily fast and 5 hours between feedings

Many individuals do not need REJUVENATOR until age 33. Prior to that, the <u>Adaptogens</u> in ADAPTO-MAX and OXY-MAX (Diphasic A.M. and Diphasic P.M.) are more critical in defense against Exogenous Aging. But at age 33, Endogenous Aging becomes THE MAJOR FORCE in the natural process of aging. And at that point, REJUVENATOR becomes essential --- at age 43 it becomes critical --- and at age 53 it becomes salvation.

Consider the four ingredients in REJUVENATOR. We have quite extensive articles on Carnosine, Lipoic Acid, Glycine and NAC --- plus Glutathione --- with countless quotes from the Literature as Gerontologists describe their benefits in maintaining health in response to Endogenous Aging.

Carnosine has sweeping rejuvenating effects --- particularly benefiting the health of the brain, the immune system, the autonomic nervous system, the cardiovascular system, and glycemic control.

As a powerful protector against INFLAM-AGING, Carnosine is a major player in both Health Span and Life Span, protecting a broad array of cellular functions that erode with aging. In fact, the term "Rejuvenins" may have been first coined by Gerontologists when describing Carnosine.

To appreciate the countless metabolic effects of Glycine --- read our write-up on this amazing nutrient. Here are a just a very few of the highlights …

FGF-21(Fibroblast Growth Factor 21) has been referred to as the "Pro-longevity Hormone". It promotes leanness, insulin sensitivity, and vascular health ------ Glycine boosts GLP-1, a metabolite that also increases FGF-21 and increases Lifespan in mice.

Glycine intake can counteract many of the adverse effects of a high-sucrose (fructose) diet on the liver, adipose tissue, and vascular function. But …

The most important role of Glycine is combining with N-Acetyl-Cysteine (NAC) intracellularly to produce Glutathione,

"The Master Antioxidant".

[Read our article on Glutathione.] Glutathione can also be thought of as "The Master REJUVENIN" --- which is the purpose of REJUVENATOR. Confirmation of Glycine's fundamental role in Glutathione synthesis is that NAC supplementation without Glycine supplementation does not raise Glutathione as effectively as does combining the two --- and Glycine alone, will raise Glutathione intracellularly. ----- Which brings us to NAC …

A DARLING OF THE HEALTH FOOD AND ALTERNATIVE HEALTH CARE REMEDY PEDDLERS ---

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for several years now. ----- DON'T believe a word they say!

To appreciate the benefits --- and the damage --- from NAC supplementation you must first realize that nearly all its effects on the Stage of Life progression -

-- from Immuno-Neuro-Endocrine Stress --- to chronic inflammation --- to INFLAM-AGING --- come from its intracellular conversion --- or failure of its conversion --- to GLUTATHIONE.

But any NAC that is not combined with Glycine to produce Glutathione can wreak devastation --- a truth that "nature cure" lovers refuse to face. Glutathione is not a disease remedy; it is a health preserver.

NAC supplementation alone will produce its desired effect of intracellular Glutathione production only to the extent Glycine is available intracellularly to combine with the NAC. NAC supplementation beyond the intracellular Glycine availability for Glutathione production becomes a major source of Reductive Stress --- and actually shortens Lifespan!!

While studies have shown life extension benefits from Glycine + NAC supplementation (--- in association with elevating intracellular Glutathione in defense against Endogenous Aging), no study has ever reported extension of life in animals or humans by supplementing NAC alone.

To illustrate the anti-INFLAM-AGING benefits of REJUVENATOR, consider just one of countless studies from the Literature: Supplementation with Glycine + NAC for 12 weeks, while comparing elderly vs. younger individuals …

At baseline, the elderly group showed 76% lower Glutathione than the younger adults, while plasma oxidative end-product concentrations were 845% higher and F2-isoprostane concentration 318% higher than the younger group. Glycine + NAC supplementation yielded a 200% increase in cellular concentrations of Glutathione, and decreases in concentrations of Oxidative Stress end-products of 74%.

Elderly subjects had fasting glucose 15% higher and insulin 469% higher, as well as insulin resistance 571% higher than in younger controls. Plasma concentrations of DNA damage markers were higher by 348%. Compared to young adults, older adults had 54% lower mitochondrial fatty acid oxidation and 51% higher mitochondrial glucose oxidation.

Glycine + NAC supplementation entirely corrected mitochondrial fatty acid and glucose oxidation --- and without affecting energy expenditure. The Respiratory Quotient showed much more efficient fat burning, and thus less dependence on sugar metabolism.

With the improvements in Respiratory Quotient --- there was a significant reduction in total body fat and in waist circumference --- showing

preferred abdominal fat loss --- an indication of improved insulin sensitivity.

Compared to younger subjects, the older adults showed extreme elevation of many pro-inflammatory cytokines at baseline …

- IL-6 was 934% higher!!! (--- Can you say, "INFLAM-AGING"?!!!)
- TNF-α was 116% higher
- C-reactive protein (CRP) was 88% higher
- Endothelial biomarkers of inflammation were as much as 175% higher

Glycine + NAC supplementation lowered IL-6 by 77%, TNF-α by 57%, and CRP by 49%, and decreased insulin by 55% and insulin resistance by 59%. (!!!)

Glycine + NAC supplementation resulted in significant improvement in both cognitive performance and physical function tests.

Lipoic Acid, like Carnosine, gives you an amazingly broad spectrum of anti-INFLAM-AGING benefits. That is why it is a critical ingredient in both your Adapto-Max and Oxy-Max, and now in REJUVENATOR.

In the context of your REJUVENATOR, Lipoic Acid, like Carnosine, performs not only its own array of benefits in maintaining the health of cells, but also functions as what Gerontologists call a ---

GLUTATHIONE INDUCER.

Glutathione production is facilitated by both Lipoic Acid and Carnosine.
(--- and also by Quercetin, FYI).

Frustrated chasing symptoms? Never again. ----- Empower patients against INFLAM-AGING. **REJUVENATOR gives you that power.**

Senescent Cell development:

CELLULAR SENESCENCE is mediated by shortening of telomeres triggering a DNA damage response in aged cells, causing growth arrest. Cell senescence can also be induced by DNA-damaging agents and activation of oncogenes.

Senescent cells exhibit a senescent secretory phenotype (SASP). Senescent cells are cells that have stopped dividing, and produce an inflammatory cocktail that contributes to age-related inflammation. The SASP cocktail consists of pro-inflammatory cytokines, chemokines, growth factors, and proteases.

Senolytics target and destroy senescent cells. Among the effective senolytics are a combination of Dasatinib (which is a tyrosine kinase inhibitor used in leukemia), paired with Quercetin, a naturally occurring flavonoid. Early phase human trials show the treatment with D + Q is associated with clinical improvement in pulmonary fibrosis, and decreases the number of senescent cells and the level of SASP.

The removal of senescent cells is shown to be a promising therapeutic approach to prevent or improve the state of INFLAM-AGING. In high fat (corn oil) diet-induced diabetes with obesity, mouse adipose tissue shows accumulation of several types of senescent cells. The senolytic combination of Dasatinib plus Quercetin reduces the number of senescent cells, improves both glucose tolerance and insulin resistance. Seno therapy in targeting mouse pancreatic β cells is validated not only in T2D, but also in T1D, and in non-obese diabetic mice as well.

Age-related metabolic dysfunction is also associated with increased adipose tissue senescent cell burden that can be reduced by senolytic administration in mice. These improvements are mediated at least in part by decreased adipose tissue inflammation, increased adipose tissue and peripheral insulin sensitivity, and enhanced ability of progenitor cells to differentiate into insulin-responsive adipocytes.

Senescent cells, particularly senescent adipocyte progenitors, accumulate in the adipose tissue of obese mice and humans, and removal of senescent cells via the senolytic drug combination D + Q improves metabolic function in obese mice. Among other senescent cell types, D + Q targets senescent human adipocyte progenitors, unlike most other senolytics.

Senescent cells also accumulate in the pancreas with aging. This β-cell senescence has been proposed to promote insulin secretion, and aged human β-cells have increased glucose-induced insulin secretion.

These findings clearly indicate that Endogenous Aging in general is largely determined by which or where senescent cells reside both in adipose tissues and in pancreatic β cells. Just as clearly, senescent cells in adipose and pancreatic cells are responsible for insulin resistance, and diminished insulin secretion.

To be perfectly clear --- as we address the process of Endogenous INFLAM-AGING, we are not proposing to treat, cure, or prevent diseases. We do not for example, treat diabetes. But, we most definitely recommend dietary supplements to individuals who are diabetic. We do so while recognizing that diabetes creates in these individuals extraordinary special needs for supplementation.

The immune threshold theory of senescent cell burden:

Senescent cells are cleared by the immune system. They can attract, activate, and anchor immune cells, including macrophages, dendritic cells, T-lymphocytes, and neutrophils through SASP chemokines, cytokines such as IL-6 and TNF-alpha, extracellular mitochondrial DNA, and other factors. However, above a threshold burden, senescent cells might interfere with the immune system and its ability to remove senescent cells.

For example, IL-6, an SASP component, interferes with macrophage migration. Senescent cells cause fibrosis that can impede immune cell infiltration and trap immune cells within Inflammatory I foci --- and, senescent cells can express "don't eat me" signals.

Based on these findings, the threshold theory is formulated. **Once senescent cell abundance is sufficient to cause spread of senescence that exceeds capacity of the immune system to keep up with clearing these cells, an accelerated aging-like state ensues.**

Consistent with this theory are the following:

1) The number of senescent cells that needs to be transplanted to cause frailty, limit Health Span, and cause premature death, including from cancer, is higher in young than old mice, and in young lean than young obese mice.

2) Old mice or young obese mice have more pre-existing senescent cells than young lean mice.

3) The abundance of pre-senescent and senescent adipose progenitors with replicative capability remains low until early old age in mice, followed by a significant increase in older mice.

So, there is a threshold above which senescent cell burden due to spread of cellular senescence becomes self-amplifying (a vicious cycle). This self-amplification could contribute to an increased risk of senescence- and age-related phenotypes, physical dysfunctions, hyperinflammation, and diseases --- perhaps contributing to age-related multi-morbidity.

Therefore, reducing systemic senescence cell burden to below a threshold might allow the immune system to clear more senescence cells, including those remaining senescence cells that are resistant to the senolytic drug administered, and to extend Health Span.

Regarding age-related osteoporosis, senescent cells accumulate in bone with aging in both mice and humans. Elimination of senescent cells in mice leads to reduced bone resorption, enhanced differentiation of progenitor cells toward osteoblast formation and increases bone strength. Based on these studies clinical trials are underway to investigate the effect of the senolytics D + Q on bone resorption and bone formation in elderly women.

More on mTor and INFLAM-AGING:

The mechanism by which mTOR plays a key role in aging is still unclear. There is evidence that mTORC1 inhibition slows aging by reducing the accumulation of proteotoxin and oxidative stress, and a general reduction in mRNA translation.

A related possibility is that inhibition of mTORC1 slows aging by increasing autophagy, which helps clear damaged proteins and organelles such as mitochondria, the accumulation of which is associated with aging and age-related diseases. [Autophagy is critical. It is maximized by a 12-hour fast from the end of the day's last feeding to the beginning of the next day's first feeding.]

Another model suggests that the attenuation of adult stem cells in various tissues plays an essential role in aging. mTOR inhibition boosts the self-renewal capacity of both hematopoietic and intestinal stem cells in mice.

----- Ultimately, the importance of mTORC1 inhibition in aging likely reflects its unique capacity to regulate such a wide variety of key cellular functions.

The importance of mTOR signaling in promoting muscle growth is well known, but the mechanisms underlying the process are poorly understood. mTORC1 activation is associated with muscle hypertrophy, and both IGF-1 and leucine promote hypertrophy through the activation of mTORC1.

While acute activation of mTORC1 does promote muscle hypertrophy in the short-term, chronic mTORC1 activation in the muscle also results in severe muscle atrophy, low body mass, and early death --- primarily due to an inability to induce autophagy in muscle tissue. Considering that turnover of old or damaged tissue plays a critical role in muscle growth, these results suggest that alternating periods of high and low mTORC1 activity, as occurs with normal feeding and fasting cycles, is essential for maintaining optimal muscle health and function.

Muscle contraction also activates mTORC1 in the muscle --- potentially explaining at least in part how increased muscle use promotes anabolism. Understanding how mTORC1 can integrate the distinct signals from insulin, amino acids, and mechanical force in the muscle will be an important goal in developing approaches for treating muscle-wasting disorders such as those associated with disuse and aging.

mTORC1 signaling also plays an important role in glucose homeostasis by regulating pancreatic β-cell function. Chronic hyperactivation of mTORC1 has a diphasic effect on β-cell function --- with young mice showing increased β-cell mass, higher insulin level, and improved glucose tolerance. This effect is reversed in older mice, which much more rapidly develop reduced β-cell mass, lower insulin level, and hyperglycemia.

Thus, high mTORC1 activity in the pancreas is initially beneficial for glucose tolerance, but also leads to a faster decline in pancreatic function over time, with diabetes the ultimate result.

This diphasic effect of mTORC1 signaling is analogous to diet-induced Type 2 diabetes progression --- in which pancreatic β-cells initially expand and produce more insulin to compensate for an increased glycemic load, but eventually undergo exhaustion.

Obese mice have high mTORC1 signaling in many tissues, including the pancreas, likely due to increased circulating insulin, amino acids, and pro-inflammatory cytokines. Increased mTORC1 signaling in these tissues also contributes to peripheral insulin resistance due to enhanced feedback inhibition of insulin signaling.

In fasting, when blood glucose drops, the liver activates a compensatory response involving the induction of autophagy, gluconeogenesis, and the release of alternative energy sources in the form of ketone bodies. Regulation of mTORC1 signaling is crucial for the response of the liver to diet.

For example, mice bred with constitutively activated mTORC1 signaling fail to generate ketone bodies during fasting. The importance of inhibiting mTORC1 in the liver during fasting is also observed in these mice that sustain mTORC1 activity during fasting, which prevents induction of autophagy in the liver, which is critical for supplying free amino acids for gluconeogenesis. As a result, these mice display fatal hypoglycemia in response to fasting.

mTORC1 promotes adipogenesis and enhanced lipogenesis in response to feeding and to insulin. This increased adipocyte formation and lipid synthesis leads to hepatic steatosis.

Similarly, the loss of mTORC2 activity in adipocytes results in insulin resistance, but also results in less lipid synthesis. mTORC2 promotes lipogenesis in the liver, as well. Thus, both mTORC1 and mTORC2 play important roles in multiple aspects of adipocyte function and lipid metabolism.

The impact of hyperactive mTORC1 in the brain can be an extreme source of INFLAM-AGING.

The importance of mTORC1 in brain tissue stems in part from its role in promoting activity-dependent mRNA translation near synapses, a critical step in neuronal circuit formation. Consistent with this finding is that NMDA receptor antagonists activate mTORC1 in mouse neurons.

The role of mTORC1 in regulating autophagy is likely also important, as autophagy dysfunction is strongly implicated in brain INFLAM-AGING.

Dietary Modification = Calorie & Protein intake:

The life-extension benefits of caloric restriction derive as much from protein restriction as from less food overall. And, the anti-aging effects of decreased dietary protein relate to minimizing just a few amino acids.

Amino Acids in general activate MTC1. In particular, Leucine and Arginine in the cytosol activate mTORC1. By a somewhat different mechanism, the amino acid Glutamine in the cytosol also activates mTORC1. Methionine is shown by much research to accelerate aging.

Restricted dietary intakes of protein or essential amino acids tends to slow aging and boost Lifespan --- presumably because they down-regulate IGF-1, and mTORC1 signaling that acts as a pace setter for aging (and promotes cancer induction). Amino acids that particularly accelerate the aging process are leucine, methionine, and arginine.

A recent analysis of the National Health And Nutrition Examination Survey (NHANES) III reveals that relatively low protein intakes in mid-life (under 10% of calories --- aka “The Okinawa Diet”) are indeed associated with decreased subsequent risk for mortality. However, in those over age 65 at baseline, such low protein intakes are actually associated with increased risk for mortality.

This finding accords well with other studies correlating relatively high-protein intakes with lower risk for loss of lean mass and loss of bone density in the elderly. Increased efficiency of protein translation reflecting increased leucine intake and consequent greater mTORC1 activity may play a role in this effect (--- however, there is no solid evidence that leucine supplementation provides important long-term benefits to the elderly).

Aside from its potential pro-anabolic impact, higher dietary protein intake may protect the elderly in another way --- by providing increased amino acid substrate for synthesis of key protective factors. ----- There is much evidence that Glutathione synthesis declines with increasing age (reflecting diminished function of Nrf2-dependent inductive mechanism) rate-limiting for Glutathione synthesis. Intracellular Glutathione blunts the negative impact of ROS on cell health, and functions both by acting as an oxidant scavenger and by opposing the pro-inflammatory influence of hydrogen peroxide on cell signaling.

Fortunately, supplementation with Glycine + NAC increases Glutathione synthesis to youthful cellular levels. Supplementation with Phase 2 inducers --- such as lipoic acid --- can also increase Glutathione.

In aging humans, Glycine + NAC supplementation has exerted favorable effects on vascular health, muscle strength, bone density, cell-mediated immunity, markers of systemic inflammation, preservation of cognitive function, progression of neurodegeneration, and the clinical course of viral infection mortality and frailty.

Thus, supplementation with Glycine + NAC + lipoic acid is significantly protective in the elderly (--- and particularly in those who follow plant-based or other low protein diets).

Immune cells and gut microbiota regulate each other reciprocally. Long-term Rapamycin administration to mice favorably alters gut microbiota in direct correlation with improvements in numbers and functionality of several immune cell populations. ----- Of course, we Nutri-Spec practitioners offer the ultimate dietary supplement --- Immuno-Synbiotic --- in our SOLID DNP to LIVE STRONGER LONGER.