

## New Discoveries Alter the Landscape Potential of Anti-Aging Therapy

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Received date: September 05, 2015; Accepted date: October 23, 2015; Published date: October 30, 2015

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### Abstract

Senescence is characterized by the decline in the ability to cope with stress. Hormesis regulation of opposing biological effects of low and high dosages, can determine longevity, and disease vulnerability at appropriate doses. Regulation of age-related changes in micro RNA opens new areas of therapeutic targets. Micro RNA downregulates stress response pathways with age establishing vulnerability to multiple age related disease which, if targeted could theoretically delay senescence. Mitochondrial targeted drugs have intervened in seemingly otherwise unrelated pathologies like neurological diseases, Alzheimer's disease, infections, diabetes, acute ischemic shock, and wound healing; an example of a common magic bullet for intervention in mitochondrial dysfunction pathologies of oxidative stress. The telomerase subunit, TERT, the promiscuous reverse transcriptase, exhibits hormetic activity, benefit at low levels, dysfunctional at high levels, and is required for signally survival. The appropriate targeted telomerase therapy is key for optimal desired drug therapy for inhibition in cancer and HIV infected therapy and enhanced in bystander cells for oxidative stress tolerance. Comparative biology studies reveal the role of Neuregulin and Nrf2, as key players in the puzzle of the long lived disease free mole rat despite high levels of oxidative stress. A hibernation stress response cold shock peptide restores synaptic plasticity, and is beneficial in neurodegeneration. Muscles and gut are not only responsible for their respective roles in locomotion and digestion but also regulate systemic responses in the body. New insights into the roles of muscles and gut change how drugs affect multiple organs and impact the route of administration. While oxidative stress can either signal metabolic benefits, death or be neutralized by a wheelhouse of antioxidant pathways, recent technological advances and conceptual shifts, allow regulation of opposing consequences by appropriate targeting of drugs to achieve protective effects in multiple age related diseases.

### Introduction

Stress tolerance capacity is a hallmark of longevity protection. Latent pathway activation of protective cascades, triggered by environmental challenges to tolerate temperature, oxygen deprivation, reactive oxygen species, and radiation can be beneficial in humans. Hormesis reflects dose dependent opposing effects of toxic agents, harmful at threshold high levels but beneficial at low doses [1]. The hormetic dose-response, represents a paradigm shift in long-standing beliefs about the nature of the non-linear dose-response in the low dose zone, as well as embraces the paradoxical roles of ROS signaling benefit versus toxic role in disease. The design of pre-clinical studies and clinical trials as well as strategies for optimal patient dosing in the treatment of numerous diseases, depends on eliciting a dose that neither is not sufficient to activate the signaling protective pathways nor is toxic [2].

Low doses of UV in *Paramecia* rejuvenated the cells and extended their lifespan, and the overarching assumption was that, an otherwise harmful agent can induce conserved beneficial pathways to extend longevity as well as tolerance to the damaging agent [3]. Likewise, environmental agents of both the cold and heat stress can increase resistance to the infection and extend life span [4,5]. Hormetic intervention has potential for benefit in aging, diseases, and health promotion [2,6,7]. Dose and frequency of exercise, as a hormetic agent can influence both heat shock proteins and strength development in aged subjects [8,9] and functions as stress response inducing agent [10]. To avoid tipping the balance from benefit to harm from improper doses of a toxic agent, mimetics of the environmental cues for therapy

are an option [10]. Stress tolerance by mimetics of hibernation offer an alternative strategy for cardiac stress intervention [11,12]. Mimetics of hibernation and exercise induce tolerance to oxidative ischemic stress in rodent models also to ischemic stress of stroke [13] and hemorrhagic shock [14-16]. While ROS is a toxic by-product of aerobic metabolism, capable of structural damage to vital essential macromolecules, ROS is as well, a physiologically required transduction signal for gene regulation and redox regulation. The recent review on redox biology in human health from life to death [17] provides essential insights into the paradoxical roles of redox signaling for life, death, and cancer therapeutics. Lessons learned from model systems of aging, i.e., *paramecia*, nematodes, rodents, bears, woodchucks, as well as other vertebrates that survive in extremes environments, offer clues to tolerance applicable for disease intervention [18]. The mole rat has critical pieces in the puzzle for prevention of existing oxidative damage from expressing the normally toxic consequences of a high oxidative milieu [19]. Recent reviews cover oxidative stress, and telomerase in mitochondria and role in longevity and health [20-23].

The review topics explored here represent paradigm shifts that impact anti-aging and related pathologies therapeutics. The topics include; 1) micro RNA as a new technology that regulates gene expression; 2) aptamers and engineered molecules that have the ability to target drugs to specific organs, cells membranes, and diseased cancer cells, Alzheimer's, and HIV cells with appropriate therapy; 3) Telomerase compartmental nuclear, nucleolar, and mitochondrial roles that can modulate dose dependent hormetic oxidative stress in disease

versus normal cells; 4) neuregulin and Nrf 2, associated with stress tolerance in mole rat long life longevity, has potential in antiaging therapy; 5) hibernation, as a model system of stress tolerance and disease intervention mimetics for human diseases; 6) muscles as a communication system secretome organ; 7) the gut and brain as a systemic hormone connection which impacts delivery of therapeutic interventions.

Together these innovations reveal that pathologies with common denominators, oxidative, insulin, chronic or acute trauma can be treated by the same drug if targeted at a dose appropriate inhibition or up regulation to intervene in disease progression and protect normal cells. Mode of administration requires proper adherence to muscles and gut role in systematic effects. In aged subjects, treatment benefit may require a longer interval for benefit. Although we always knew that exercise and diet were important, the innovation in new technologies, accentuate their importance with sound scientific foundations for their role in aging and disease vulnerability.

MicroRNAs are small non-coding RNAs that can dictate expression of survival and longevity pathways found in plants, animals, and viruses involved in RNA silencing and post transcriptional regulation of gene expression. The microRNAs are generated from double stranded RNA, processed, and loaded onto a complex RNA-induced silencing complex (RISC) which is directed to a mRNA with the complementary homology target sequence with the ability to silence the expression of that gene transcript [24,25]. Identification of multiple microRNAs is identified and is emerging as drug targets for intervention in senescence and multiple diseases [26-39]. Senescence and age-related diseases are characterized by vulnerability to oxidative stress and immunosuppression. MicroRNAs that principally target genes associated with the immune inflammatory response and cell-cycle arrest were identified in the kidney [33]. Renal specific microRNAs were found that promote renal senescence by suppression of mitochondrial antioxidants, superoxide dismutase 2 and thioredoxin reductase and thereby promote kidney senescence. By using interfering siRNA, complimentary to these suppressive microR-335 and microR-34, senescence of old mesangial cells was inhibited via upregulation of antioxidants SOD2 and Txnrd2 with a concomitant decrease in ROS [33]. The possibility that aging could be halted by antisense homology siRNA and prevent downregulation of stress resistance pathways by suppression of specific microRNAs provides the "magic bullet" possibility to delay multiple age-related oxidative stress related disease progression.

MicroRNAs show intervention potential in neuroprotective intervention in Huntington's disease [34] and in Alzheimer's disease [35,36]. Non-coding RNAs are recognized as regulators of skeletal muscles in development and diseases [37]. The interaction of senescence pathways in mitochondrial biogenesis, telomere attrition, and epigenetic interactions by microRNAs have been recently reviewed as master switches, and provide the promise of target directed intervention in aging and cancer [38,39].

A recent study explored the role of a transcribed long-non-coding RNA in aging endothelial cells, and identified ASncmtRNA-2. Endothelial cells from aortas of aged mice revealed increased levels of ASncmtRNA-2. The cell cycle inhibitor p16 gene also showed expression of the same ASncmtRNA-2 sequence. Identified microRNAs, has-miR4485 and has-miR-1973, had perfect homology to the double stranded region of ASncmtRNA-2. Endothelial cells overexpressing ASncmtRNA-2 showed accumulation of cells in G2/M phase, suggesting a direct role of microRNAs in replicative senescence

[40]. In hibernation, microRNA shows adaptive changes and may be pivotal if specific microRNAs are identified to affect adaptive stress to promote stress tolerance [41].

Aptamers are small molecules isolated from nucleic acid libraries with desired selective binding properties [42] to provide an "address" for drug delivery. The aptamer targeted oligonucleotide therapeutics to allow site specific delivery for interference or promotion of metabolic network to alter disease pathology [42-44]. SiRNA chimeras are available for HIV [45,46] and Alzheimer's disease [47]. In Alzheimer's disease pathology, amyloid targeted peptides can inhibit toxicity [48] and amyloid aggregation [49]. Curcumin loaded-PLGA nanoparticles conjugated with Tet-1 peptide are available to bypass the blood brain barrier to deliver the strong antioxidant properties of curcumin [50]. Fluorescently tagged anti-RNA aptamer  $\beta$  55 which binds to amyloid plaques allows optical imaging agents for amyloid plaque detection both in vivo human Alzheimer's brain tissue, and in vivo transgenic mice [51] aids in early detection of Alzheimers disease, at a time when available therapeutics may halt the progression of the disease. Mitochondrial targeted aptamers are identified to deliver drugs directly to mitochondria and intervene in mitochondrial dysfunction related diseases [52]. Targeted catalase to mitochondria, not to the nucleus or peroxisome, in transgenic mice established the importance mitochondria in delay of age related diseases and increased longevity [53].

Antioxidant agents engineered or discovered by accident represent a class of mitochondria targeted therapeutic drugs. Mitochondrial targeted agents can be conjugated to known redox agents to triphenylphosphonium ion (TPP+) with coenzyme Q (MitoQ) and plastoquinone (SkQ1) [23,54,55] to neutralize mitochondrial oxidative stress in pathology and prevent senescence. A review of the Szeto-Schiller (SS) compounds, which were serendipitously found to preferentially concentrate in the inner mitochondrial membrane, have intervention potential in multiple diseases [23].

The discovery that mitochondrion is a direct site of A beta accumulation in Alzheimer's disease [56] highlighted mitochondria as the source of free radical generation and oxidative damage in disease progression. Mitochondrial targeted catalase was found effective in reducing oxidative damage in a mouse model of Alzheimer's disease and likely in other neurological disorders [57]. The antioxidant mitochondrial SS31 prevents mitochondrial abnormalities, and synaptic degeneration in Alzheimer's disease [58]. The mitochondrial targeted drug was neuroprotective in Parkinson's disease mode [59]. RNA silencing of genes affected by Alzheimer's disease, enhance mitochondrial function and synaptic activity in Alzheimer's disease model [60]. Cell-permeable antioxidants targeted to mitochondria promote protection of mitochondria, oxidative toxicity in reperfusion, injury as well [61,62]. Mitochondria-targeted antioxidant SkQ1 improves insulin resistance [63] and impaired dermal wound healing in old mice [64]. Targeted antioxidant, therapy then, shows promising intervention reduction in Alzheimer's disease toxicity, in Parkinson's disease, reperfusion injury, diabetes and wound healing, demonstrating the far reaching benefit of targeted antioxidant therapy in intervention in different pathological scenarios [23]. Side effects emerged with undesirable effects in cell bioenergetics [65-67], as might be anticipated from predicted interference in ROS signally benefits. The intervention in multiple diseases by targeted antioxidants demonstrate that mitochondrial dysfunction and oxidative stress within mitochondria is a common denominator in disease progression and can be treated by common drugs for intervention in diseases.

Examples of supplements known to protect cell structure or to activate protective metabolic networks include lipoic acid, carnitine, and resveratrol. Lipoic acid has antioxidant activity that preserves the structural and functional integrity of RBC in diabetes. The RBC can then assume a more efficient role as the first line of systemic defense against diabetic complications arising from oxidative stress-induced damage [68, 69]. Acetyl-L-carnitine induces upregulation of heat shock proteins and protects cortical neurons against amyloid-beta peptide mediated toxicity and thus is nutritional candidate for intervention in Alzheimer's disease [70]. Resveratrol may target activation of the SIRT-1/PGC-1 neuroprotective axis. Modulator of cellular stress response in health and disease states of carnitine and acetyl-L-carnitine in mitochondrial dysfunction, aging, and age-related disorders [2,70]. A mushroom extract was found protective of pancreatic islets and may have potential in diabetes [71]. A complete list of potential antioxidants or beneficial supplements is well beyond the scope of this review.

Telomerase is almost universally conserved in eukaryotes [72] signifying its essential role in survival strategies. Telomerase is promiscuous in multiple cellular regulatory roles controlling survival pathways by translational and transcription interactions, and chromatin modification that each impact cell survival, albeit by separable mechanisms described below, including responses to oxidative stress. Telomerase is a reverse transcriptase TERT, a subunit catalytic protein with an RNA ligand TERC functions as an RNA dependent DNA polymerase, capable of replacing tandem short DNA sequences at telomere ends of eukaryote chromosomes [73]. In its telomere maintenance capacity, telomerase is recognized as a major deterrent to replicative senescence and decline of function with age. Telomere dysfunction induces metabolic and mitochondrial compromise, activates p53-mediated cellular growth arrest, senescence and apoptosis to drive progressive atrophy and functional decline in high-turnover tissues [74]. The reversal of tissue degeneration in aged telomerase deficient mice by genetically engineered inducible telomerase activation shows unprecedented evidence for the major participation of telomerase in regeneration and rejuvenation of organ systems [75]. Telomerase deficiency impairs glucose metabolism and insulin secretion [76]. TERT, the telomere reverse transcriptase catalytic subunit promiscuous protein can partner with a different mitochondrial RNA ligand, RMRP to transform its function into the only known RNA dependent RNA polymerase, the only enzyme identified in eukaryotes. The double stranded RNA can be processed into small interfering RNA siRNA in a Dicer-dependent manner, thereby establishing a mammalian RNA dependent RNA polymerase [77]. Since small interfering RNA are capable of regulating gene expression, mitochondrial based regulation of gene expression is a reality [77]. TERT is positioned at the crossroads of aging, disease, senescence and health in recent reviews [20-23] that document the role of TERT in mitochondria and oxidative stress. Since mitochondria are critical determinants in survival, mitochondrial TERT emerges as a prominent denominator in response to disease and target for therapy. In response to oxidative stress, TERT protects mitochondria [78-82] and unfortunately protects cancer cells [80] by inhibiting apoptosis via association with BCL-1 pathway [83]. TERT protects developing neurons from cell death after DNA damage [84]. The finding that TERT exacerbates mitochondrial toxicity [85] is not yet resolved with the other studies showing the protective role TERT. TERT regulates gene expression at different levels. At the levels of translational control of the cell cycle, TERT inhibits p15INK4B [86], by chromatin modifications. TERT regulates Wnt signaling [87], and induces a DNA

damage repair response [88]. TERT also participates in the transcriptional control of the Myc-Wnt developmental program [89]. TERT Wnt/catenin signaling in stem cells [90] exerts master regulation in multiple different stress response pathways. TERT operates in reciprocal transcriptional control of NF kappa B [91]. Importantly, Nf kappa B can also regulate TERT as well in reciprocal interactions [92]. The interactions of TERT in multiple pathways can be isolated genetically [93]. TERT regulation may be targeted to achieve separate desired therapeutic goals.

In diseases, telomerase overproduction represents the dark side in cancer progression and HIV infection and is a successful target in disease intervention. An immune approach to develop a cancer vaccine is based on activation of the immune response system with tumor-reactive peptides that were derived from telomerase tumors, to destroy cancer cells [94,95], and is an approach that may be effective in HIV therapeutics as well.

Disease damage shows the consequences of TERT deficit. The hippocampus of Alzheimer's disease brains, and in cultured neurons, shows oxidative stress damage. The absence of TERT increases ROS generation and oxidative damage in neurons induced by pathological amyloid  $\beta$  peptide induced apoptosis [96,97], ischemic brain injury, neurotoxicity [98]. TERT presence was associated with promotion of neuronal survival in the developing rat brain after hypoxia-ischemia, including enhancement of neurotrophin-3 expression in astrocytes [99]. Using a TERT enhancing agent can promote delay of the onset of amyotrophic lateral sclerosis, and suggests therapeutic increase of TERT in TERT deficient pathologies [100]. Nitric acid can activate telomerase and delay endothelial senescence [101] and has therapeutic potential.

A paradigm shift in the dose dependent hormetic effects of TERT at low dose, and dysfunction at high dose impacts therapeutic strategies in disease intervention. Telomerase involvement in oxidative stress in diabetes, Alzheimer's disease, wound healing, chronic cardiac dysfunction, acute stresses of heart attack, stroke, and hemorrhage requires telomerase enhancement in normal bystander cells, while telomerase inhibition is required in cancer and infected cells. Targeted therapy allows selective disease therapy.

The naked mole rats (*Heterocephalus glaber*) emerge as major player in providing puzzle pieces in longevity determination, and the role of neuregulin in longevity. The extremely long-lived species inhabit an underground hypoxic environment, and despite high levels of oxidative damage, and hypoxia inducible factor HIF-1, live a long life without neurological pathology and cancer despite short telomeres [102, 103]. All the secrets to oxidative tolerance are elusive but recent studies reveal important clues to its tolerance to high oxidative stress. Protein stability and resistance to oxidative stress were found to be determinants of longevity in the longest-living rodent, the naked mole-rat [104]. Neuregulin-1 emerges as a critical determinant of longevity [105]. Neuregulin positively correlates with lifespan in divergent species, and is critical for normal brain function during both development and adulthood in the naked mole rat [105].

Neuregulin is known to modulate muscle metabolism and insulin sensitivity [106,107], and neurotoxicity [108]. Neuregulins are multitasking master regulator that function as a myokines, participate in myogenesis, muscle metabolism, and may function for the rapid and chronic metabolic effects related to muscle contraction, including improvement in insulin sensitivity and maintained in the mole rat and old animals [108]. In a manner analogous to insulin and exercise,

neuregulins stimulate glucose transport through recruitment of glucose transporters to surface membranes in skeletal muscle. Like muscle contraction, neuregulins have additive effects with insulin on glucose uptake [108]. Neuregulin-1 also exerts protective effects against neurotoxicity and development and plasticity [107]. The rapid and chronic metabolic effects of neuregulin appear to be related to muscle contraction. The effects of neuregulin resemble those of exercise, by improvement in insulin sensitivity, preservation of energetic metabolism, and insulin responsiveness [106-108]. Neuregulin is target for up regulation in age-related therapy and down regulation in cancer.

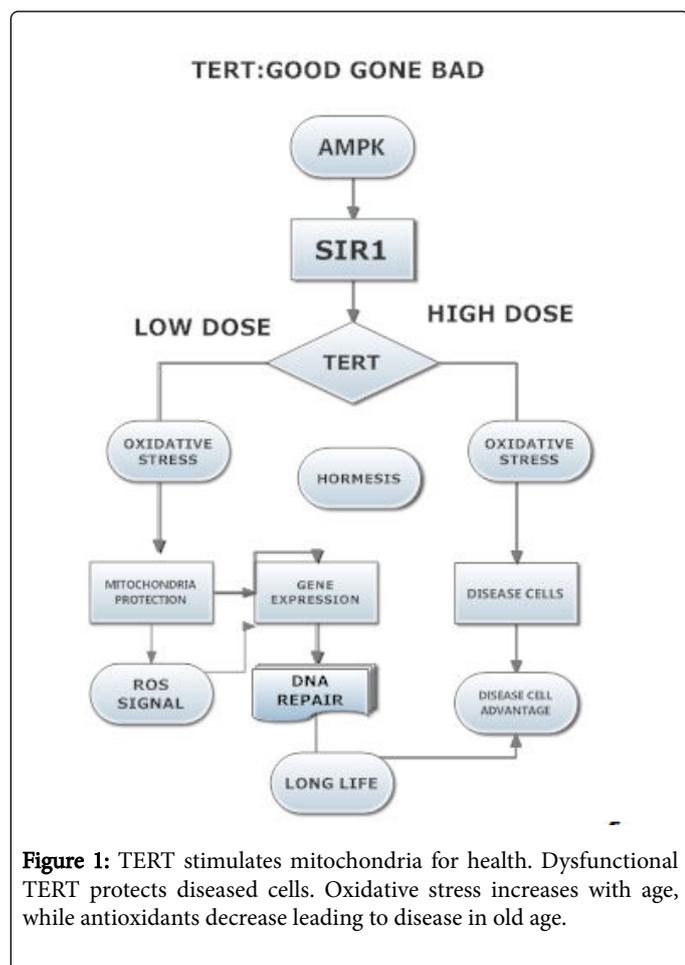
with a gene mutation deletion of mitochondria Superoxide dismutase-2 [110]. Mitochondrial and cytoplasmic ROS have opposing effects on lifespan [110,111], a discovery that emphasizes the role of positional effects of regulators of ROS on longevity, and a “plan B” for other cytoplasmic regulators of damage.

Hibernation is a classical beneficial response to environmental stresses of depleted energy stores, intracellular acidosis, hypoxia, hypothermia, cell volume shifts, and inactivity induced muscles wasting [112], that mimic markers of the senescent phenotype. Changes in hibernation include upregulation of key regulators of energy metabolism and mitochondrial biogenesis [41,113,114] including PPAR gamma transcription factor and its coactivator, PGC. Delta-2 opioid receptor agonist, a mimetic of the Hibernation Induction Trigger, activates protection in models of ischemic stress in rodent model systems of heart attack [11,12], stroke [13], and hemorrhagic shock [14-16] and could be effective in Alzheimer’s disease pathology [115]. The delta-2-opioid agonist shows inhibition of p38 MAPK [116], and may be protective in brain associated injury. The p38 delta opioid receptor agonists show HIV intervention potential in HIV pathologies [117,118].

Another hibernation stress tolerance to cooling damage and reheating has potential anti-aging clinical applications [119]. Cooling and hibernation induce a number of cold-shock proteins in the brain, including the RNA binding protein, RBM3. While cooling induces the loss of synaptic contacts, the synaptic contacts reform with rewarming in artificially cooled normal rodents, while mouse models of neurodegenerative disease were impaired in the rewarming response unless supplemented with RBM3 lentiviral delivery. RBM3 protected synaptic loss, behavioral deficits, and prolonged survival, while knock out of RBM3 exacerbated synapse response. These experiments provide evidence of the potential benefit of RMB3 in neurological disease and other protein structure dysfunctions, resulting from oxidative damages in diabetes and viral infections [119].

AMPK is a known as the master regulator of energy [120,121]. The AMP-activated protein kinase (AMPK) is a sensor of energy status that, when activated by metabolic stress, maintains cellular energy homeostasis by switching on catabolic pathways and switching off ATP-consuming processes. AMPK is also crucial in regulation of whole body energy balance, particularly by mediating effects of hormones acting on the hypothalamus [121]. AICAR, a mimetic of exercise, triggers the signal that the cell pathway needs to be replenished [121]. The AMPK-PPAR pathway activation by oral administration of AICAR can enhance training adaptation or even can increase endurance without exercise [121], and improve tolerance to hemorrhagic shock [16]. Age-associated reductions in AMPK activated kinase and mitochondrial biogenesis, responded to AICAR treatment [122-124]. AICAR administration benefited motor and cognition function in young as well as in aged mice via a muscle mediated pathway [123,124]. Earlier attempts to alleviate energy loss, by AICAR in elderly [122] may be due to route of drug delivery.

A longer duration of AICAR treatment in old animals, 14 days in old versus just 3 days in young animals, induced the positive exercise response with improved water maze, rotarod, and open field parameters that correlated with increased neuronal and plasticity gene expression in both the hippocampus and muscle [123,124]. Pronounced upregulation of mitochondrial genes in muscle and brain, relative to neuronal development and plasticity, were enriched in the hippocampus. Age, duration of treatment, and route of administration appear to play an important role in the effects of AICAR on behavior,



A key member of the neuregulin pathway is the nuclear factor erythroid factor 2 (Nrf2) that regulates the transcription of several hundred cytoprotective molecules, including antioxidants, detoxicants, and molecular chaperones, heat shock proteins. The Nrf2 itself is tightly regulated by mechanisms that either promote its activity or increase its degradation. Nrf-2 is regulated in the mole rat and maintained though out its long life time [109]. Constitutive Nrf2-signaling activity is significantly linked with increased maximal lifespan, not linked to the protein levels of Nrf2 itself, but rather with down regulation of proteins that target Nrf2 for degradation [109]. These mole rat studies highlight Nrf2 as an anti-aging molecule, and the strategy to target degradation pathways of key antiaging regulators in other systems.

Nematode mutants share with mole rats, the ability to have extended life span with an “excess” of oxidative damage, associated

since alternative routes were not effective [124]. The results demonstrate that the AMPK agonist AICAR can increase spatial memory and improved motor function likely mediated by muscle mediated pathways, since female transgenic mice with a muscle-specific mutated AMPK  $\alpha$ 2-subunit, did not respond to AICAR [123]. However, recent studies with young mice found the beneficial muscle and brain effects, but found an adverse effect of AICAR on the brain, after 14 days, raising concern about AICAR long term use [125]. It is well known that exercise stimulation of brain is important in health maintenance [126-128] and exercise studies exemplify molecular foundation for the critical role of exercise as therapy in aged humans.

The concept that the muscle is not only a locomotor unit, but rather is a secretome organ that releases several hundred secreted peptides that communicate throughout the body [129,130]. Multiple muscle functions represents a paradigm shift for understanding how muscle connections can impact adipose tissue, liver, pancreas, bones and brain [129,130]. Muscle induced myostatin, LIF, IL-6 and IL-7 affect muscle hypertrophy and myogenesis, BDNF neurotrophic factor affects the brain. IL-6 is involved in AMPK-mediated fat oxidation with systemic on the liver, adipose tissue and the immune system, and mediates crosstalk between intestinal L cells and pancreatic islets. Other myokines include the osteogenic factors IGF-1 and FGF-2. FSTL-1 probably leads to an altered myokine response, and the association between sedentary behavior and many chronic diseases [129,130]. The strongest molecular relationship of exercise and functional connectivity was identified for brain-derived neurotrophic factor, BDNF, as well as the role of exercise and energy intake as a determinant of vulnerability to injury a disease [128-130]. Exercise appears to be a universal protective therapeutic agent with positive whole body benefits.

Liraglutide, a long-acting glucagon-like peptide-1 hormone (GLP-1) analogue resistant to degradation is marketed as an anti-diabetes drug. Insulin resistance is a common dominator in diabetes and neurodegenerative diseases [130]. The gut secreted hormone with insulinotropic activity, promotes glucose hemostasis and shows treatment potential for multiple organ pathologies that share insulin resistance, beside diabetes. Alzheimer's and neurodegeneration diseases exhibit positive and protective effects in several different tissues, including pancreas, heart, and brain, by promotion of glucose homeostasis when oral, but not intravenous glucose administration stimulates GLP-1 secretion [130]. The gut glucagon like peptide, GLP-1 actions depend not only on the direct effect mediated by its receptor activation, but also on the gut-brain axis involving an exchange of signals between both tissues via the vagal nerve, thereby regulating numerous physiological functions in energy homeostasis, glucose-dependent insulin secretion, as well as appetite and weight control with insulin tropic activity [130]. Previous studies of type 1 and 2 diabetes [131] GL1 and GLP2 biology [132] supplement the role of the gut and diabetes biology.

Importantly, several preclinical studies showed anti-apoptotic, anti-inflammatory, anti-oxidant and neuroprotective effects of liraglutide against type 2 diabetes, stroke and Alzheimer's disease (AD), whereas several clinical trials, demonstrated some surprising benefits of liraglutide on weight loss, microglia inhibition, behavior and cognition, and in AD biomarkers [129-131].

## Discussion

The ability to withstand oxidative stress is regulated by: 1) reducing the amount of ROS produced; 2) neutralizing the ROS that is produced but not before low levels induce beneficial pathways; 3) appropriate targeting ROS in mitochondria, versus cytoplasmic ROS; 4) avoiding toxic effects of high levels of oxidative stress without fallout of diseases and lifespan reduction. The environment, lifestyle, and attitude can alter the amount of oxidative damage, pollution, job choices, and perception of stress. Antioxidant networks have dose dependent beneficial signaling, and "backup" plans, in different species, mutations that reveal use of pathways residing in different intra cellular cytoplasmic compartments.

Despite the central role of mitochondrial determination of lifespan and diseases vulnerability, other cytoplasmic compartments and gene expression regulator, miRNAs are now visible in the senescent landscape. The ability to tolerate high levels of oxidative stress such the phylogenetically diverse species, the mole rat and nematode, birds, and bats, emphasize the potential of humans to adapt to extreme life style demands. Recent studies reveal the long-lived rat has high oxidative damage in youth that does not increase with age, has protective pathways sustained with age, due to decreased degradation of the protective Nrf2. The nematode as well has high oxidative damage in youth and increased longevity. It seems that adaptation to high stress in youth by "backup protective pathways", that are maintained with age, represent a desired healthy longevity- promotion strategy that may be used to promote human resistance to age-related diseases.

## Summary

Oxidative stress can signal required metabolic benefits, kill diseased cells, be neutralized by a wheelhouse of antioxidant pathways, and be tolerated. Now, technological advances allow the ability to capitalize on the separation of opposing functions of oxidative stress, by the use of targeting drugs to achieve the desired goals, i.e., inhibition of TERT overexpression in cancer and HIV diseased cells, enhanced TERT in protection of normal cells. MicoRNAs, known to down regulate age-related stress tolerance, may be targeted and delay senescence onset, or intervene in specific organ diseases. Master regulators, TERT, Neuregulin, Nrf-2 and AMPK regulation pathways and miRNAs have associations that control oxidative stress responses that are sensitive to appropriate hormetic signals and mimetics of stress response triggers. Multiple pathologies, with ischemic stress, or insulin resistance can be treated by the same drug. The muscle and gut brain connections throughout the body via myokines and hormones revolutionize concepts of the importance of oral, intraperitoneal, or intravenous delivery can determine outcome of treatment. Age, duration of treatment, mode of delivery, and dose, are critical variables in drug outcomes on health and age related disease management.

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