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From genoprotection to rejuvenation

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1. ABSTRACT

Aging results from aberrations in signaling mechanisms and decline in biologic activities and cellular functions. Anti-aging strategies include a number of dietary, genetic, and pharmacological interventions that converge on a core network of nutrient sensors including AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), the insulin/insulin-like IIGF) growth factor signaling pathway (IIS), sirtuins, NFκB, and FOXO. Aging can be delayed and life-span and health-span can be extended by calorie and dietary restrictions, administration of NAM, NMN, NR, NAD$^+$, and by antioxidants including hydrogen sulfide. Additional measures for the age related decline in tissue homeostasis include senotherapeutics, senolytics, senomorphics, anti-inflammaging strategies, reactivation of telomerase and prevention of stem cell exhaustion. There is also a possibility to erase the signs of aging and even to reverse aging by epigenetic reprogramming and other emerging measures.

2. GENOPTORECTION STRATEGIES

Chronological aging is caused by aberrations of diverse transcriptional programs and cell signaling pathways which alter the tissue and organ functions during aging. It has been shown that a number of environmental and nutritional changes including dietary, calorie, and protein restriction can delay the inevitable consequences of aging and that life might be extended in experimental animals including *Drosophila melanogaster*, *Caenorhabditis elegans* (*C. elegans*), to mice and even in humans (1-4). Moreover, alterations of signaling pathways that deteriorate by aging have been shown to be

restored by introduction of genetic changes in yeast, flies and worms (5-6).

2.1. Calorie and dietary restriction and interventions

Some of the effects of calorie restriction (CR), AMPK and calcineurin appear to be due to the blocking of CRTC–CREB pathway (7). A complete removal of food has been shown to extend life-span in *C. elegans* (8-9). The beneficial impact of dietary restriction (DR) can be achieved by reducing nutrients, or by reducing total protein or the essential amino acids (EAA), or merely by reducing the sulfur amino acids (SAA) in the diet. It is thought that the amino acid sensors, GCN2 and mTOR, are involved in the beneficial effects of restriction of protein or selective amino acids in life extension (10). The effects of CR on longevity also seems to be attributable to the restriction of proteins or specific amino acids (11). For example, the restriction of the amino acids serine, threonine and valine, in yeast promotes stress resistance and longevity (12). As compared with glucose restriction, withdrawal of protein from the diet had a much greater effect on life-span in *Drosophila melanoganster* (13). Restricting tryptophan also appears to increase longevity in rats (14-15). Five fold reduction of L-methionine in the diet was associated with lower levels of IGF-1, insulin and glucose and a higher resistance to liver injury, and an increase in the life-span by 30% in male rats (16-17).

The extremely high life expectancy in centenarians in Okinawa, Japan may well be due to 17% lower average daily food intake of a diet, that is low in proteins and rich in vegetables, fruits and fish as well as consumption of foods which are rich in monounsaturated and polyunsaturated fatty acids (18-19). Mediterranean diet, which is rich in monounsaturated and polyunsaturated fatty acids, and is considered to promote longer telomeres, and healthy aging, reduces mortality from cerebrovascular accident (CVD) (11, 20-23). Consistent with these findings, higher intake of n-3 polyunsaturated fatty acids supports lower cognitive decline and a better cognitive performance in individuals who are on Okinawan or Mediterranean diets (24-25). CR has been shown to lower core body temperature, to reduce total and visceral fat, to improve the glucose tolerance, insulin action, adipokine, adiponectin, leptin, inflammation and interleukins, to decrease energy expenditure and loss of muscle mass and strength and to extend life-span in different model organisms (26-30). Classic CR regimens in rodents involves restriction of total food intake by 20–60%, by reducing the overall calorie intake (calorie restriction), or by intermittent or every-other-day fasting. CR attenuated the age-related increase in oxidative stress and decline in autophagy in rat skeletal muscle and induced a lower decline in insulin sensitivity in the rat liver (31-32). Intermittent fasting also improved regulation of glucose homeostasis and led to a 40% reduction in the IGF-1 levels (33-35). At least 60% of the CR group animals had less age related damage and lived longer than those that were fed *ad libitum* (36). Such diets offer overlapping functional benefits on stress resistance, metabolic fitness and life-span (37-39). There is substantial evidence that metabolism and aging are linked and that adoption of less active metabolism can prolong life for an extended period of time. One idea that arose over 70 years ago by McCay in studying rats subjected to CR, is that the decline in the supply of the food, evokes stress-resistance programs, and delays or suspends reproduction until such time that the environmental factors change and food supply is restored. These results have been repeatedly confirmed (40-44). Studies in model organisms including *C. elegans*, mice and non-human primates have repeatedly shown that CR is a promising tool in fight against aging and age related pathologies (45). In non-human primates, 30% CR led to lower incidence of age-related diseases, less loss of grey matter and improved survival, yet, these findings are at odds with a study carried out at the National Institute of Aging (NIA) study on rhesus monkeys (46-47).

CR and DR, reproducibly extend the maximum life-span in mammals, likely, by activating a biological defense response that helps organisms to survive in case of environmental adversity (48). For example, yeasts can live longer in mildly stressful conditions such as low nutrients, osmotic stress, high temperature and high salt (49-51). Together, the engagement of such defense systems have shown to extend the life-span of yeast, flies, nematodes, and

rodents (2, 52-57). In primates including humans, CR has been associated with a significant improvement in physiological functions including fasting insulin level and 24-hour energy expenditure (53,58-62). Experiments in short lived organisms such as nematodes and flies have revealed that the calorie restriction works by modifying the insulin signaling, nutrient sensing and chromosome remodeling and engages the systems that are directed at damage response pathways (5). Oxidative stress leads to a significant age dependent increase in 8-oxo-2-deoxyguanosine (oxo^{8}dG) levels in nuclear DNA (nDNA) in all tissues and increase oxo^{8}dG in mitochondrial DNA (mtDNA) in liver of rats and mice. DR is likely to decrease ROS production and has been shown to reduce the rate of DNA damage as evidenced by accumulation of oxo^{8}dG in various tissues (63-64). The efficacy of CR, particularly interventional clinical trials and the mode of such treatments for increasing health-span and life expectancy in humans, are still required before such strategies can be successfully implemented in humans.

2.2. NAM, NMN, NR, NAD$^+$ and metformin

The flow of carbon and energy occurs through glycolysis and mitochondrial oxidative phosphorylation (OXPHOS). These reactions require a tightly controlled balance between the synthesis and degradation of nicotinamide adenine dinucleotide (NAD) or NAD$^+$ in cells. NAD$^+$ is an important co-factor in all living cells and is essential to life in biological processes as diverse as production of ATP via anaerobic glycolysis, tricarboxylic acid cycle metabolism (Krebs cycle), OXPHOS, fatty acid β-oxidation, cell signaling, gene expression, and DNA damage repair by NAD$^+$-dependent sirtuins (65-71). In mammals, NAD$^+$ is synthesized from one or more of its major precursors including tryptophan (Trp), nicotinic acid (NA), nicotinamide (NAM), nicotinamide mononucleotide (NMN), and nicotinamide riboside (NR). In mammals, NMN is a natural compound and an efficient NAD$^+$ precursor and is synthesized from nicotinamide, by the rate-limiting enzyme, nicotinamide phosphoribosyl transferase (Nampt) from nicotinamide, and 5′-phosphoribosyl-1-pyrophosphate (PRPP), or from NR by NR kinases (NRKs) by phosphorylation reaction and then it is converted to NAD$^+$ by NMN adenylyl transferases (NMNATs) (68).

The deacetylase activity of the sirtuin proteins and metabolic homeostasis is dependent on NAD$^+$ (72-76). NAD$^+$ is also required for metabolism and the actions of poly(ADP-ribose) polymerase proteins (PARPs), namely PARP1 and PARP2 in mammals, and acts as a DNA damage sensor for these polymerases, in the processes of protein deacetylation and poly-ADP-ribosylation (PARylation) (77-80). PARP-1 is a NAD$^+$-dependent ADP-ribosyltransferase, that oscillates daily by feeding. It has been shown that PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation whereas PARP2 regulates SIRT1 expression and whole-body energy expenditure (81-82). Consistent with NAD$^+$ being required for PARP action, inactivation of PARP1 increases tissue NAD$^+$ levels and activates mitochondrial metabolism (81). Interestingly, there is some evidence that links the PARPs to increase in life-span (83-84).

It has been shown that the level of NAD$^+$ drops with age in *C. elegans* and aged mice and such a decrease reduces longevity in *C* and conversely genetic or restoration of NAD$^+$ levels prevents metabolic changes associated with aging and leads to increased life-span in *C. elegans* (85-86). In this nematode, increase in levels of NAD$^+$ by PARP inhibitors leads to the improvement of mitochondrial homeostasis through the activation of the sirtuin homolog, sir-2.1 and leads to the activation of the mitochondrial unfolded protein response (UPR^{mt}), which is a mitochondrial proteostasis pathway, known to promote longevity (87-89). This increase also leads to the activation of the FOXO transcription factor, *daf-16,* triggering an antioxidant protection program (85, 90).

In mammalian cells, the principal substrate for the synthesis of NAD$^+$ is the nicotinamide (NAM) salvage pathway which requires sequential actions of nicotinamide phosphoribosyltransferase also known as pre-B-cell colony-enhancing factor 1 or visfatin (Nampt) and NMN adenylyltransferases (NMNAT1-3) leading to the production of NAD$^+$ from NMN and ATP (91). Thus, NAM is a requisite precursor for the

synthesis of NAD^+, a key molecule that maintains SIRT1 activity, energy metabolism, and metabolic homeostasis (68-69, 92-95). Aging and age-related diseases, including metabolic disorders, cancer and neurodegenerative diseases all result in reduced intracellular NAD^+ levels due to reduced synthesis and increased in its consumption. It has been shown that administration of NMN to rodents enhances the biosynthesis of NAD^+ in many tissues. Also, the administration of NAD^+ precursors, such as NAM, or nicotinamide riboside (NR) is an efficient way to substitute the lowered levels of NAD^+ that occur with age. In a mouse model of obesity, NAM has been shown, when added to a standard diet, to restore glucagon storage and to ameliorate diet-induced hepatosteatosis, oxidative stress and inflammation that is seen in age-matched mice (96). NAM improves mitochondrial function, prevents age and high fat diet induced DNA damage and inhibits formation of glucoma (96-97). Loss of NAD^+ can also be effectively remedied by long-term oral administration of NMN (up to 300 mg/kg) that has been shown to increase NAD^+ in various peripheral tissues in mice without causing toxicity, an strategy that offers protection against age induced functional decline as evidenced by erasing age-related changes in gene expression and adipose tissue inflammation and for replenishing energy stores, re-establishing insulin sensitivity, restoring mitochondrial oxidative and lipid metabolism, and in maintaining the eye and immune functions and bone density (68, 93, 98-108).

Overexpression of the mitochondrial *Nmnat3* in mice, which is required for NAD^+ biosynthesis, improves age induced glucose tolerance and high-fat induced obesity (109). NMN has been shown to prevent age related metabolic dysfunction, to increase insulin secretion and sensitivity and to normalize glucose tolerance in a host of conditions. NAD^+ dependent improvements in health-span has been shown in normal aging mice, *Nampt*$^{+/-}$ mice, β cell-specific *Sirt1*-overexpressing (BESTO) mice, age or diet-induced diabetes, and hypomorphic BubR1 (a mitotic check-point kinase) mice (68, 93-98, 108). In the *C. elegans* model of xeroderma pigmentosum group A, ataxia telangiectasia, that is caused by mutation in *ATM*, a master regulator of DNA damage response and which leads to severe neurodegeneration, NMN, affords protection against premature aging and extends life-span and health-span (85, 104, 109-117).

Treatment of mice with NMN (up to 300 mg/kg) has revealed no toxicity and NMN has been shown to readily pass the blood brain barrier increasing the NAD^+ levels in the brain tissues (118-120). In animal models of aging, long-term administration of NMN maintains lipid and energy metabolism, increases insulin sensitivity, protects the eye and immune functions, bone density and affords protection in the animals against age-associated functional decline (108). Administration of NMN reduces inflammation, improves mitochondrial function in arterial and skeletal muscles, maintains neural stems and progenitor cell population, prevents synaptic loss and protects aged mice against neuronal cell death, pathological damage by Alzheimer's disease associated β-amyloid (Aβ), cognitive function, and neurodegeneration (121-126). NMN protects the heart and brain against ischemia-induced damage (127-128).

In the salvage pathway, NR, a natural precursor of NAD^+, is converted into NMN by NRKs. NR protects against aging and age-related diseases, decreases weight gain and obesity, and improves glucose tolerance. In models of diabetes and high-fat diet, NR improves metabolic function and reduces fat deposition and increases life-span and health-span in many model systems (85, 129-137). Replenishing NAD^+ stores, by administration of 400 mg per kg NR, improved muscle function and reduced heart damage in mdx and mdx/Utr$^{-/-}$ mice and reversed pathology in *C. elegans* models of Duchenne Muscular Dystrophy (DMD) (138). Nampt skeletal muscle knockout mice show 85% decline in intramuscular NAD content, muscle fiber degeneration and progressive loss of muscle strength and exhibit a reduced treadmill endurance. In this model, the supplementation of NR, despite having a modest effect on the intramuscular NAD levels, reversed these functional deficits and restored muscle mass (139). NR has been shown to improve the mitochondrial proteostasis and functions and to maintain motor functions. NR also delayed the decline in cognitive function, improved learning and memory, and reduced the neuronal cell death in

animal models of AD and Parkinson's disease (PD). In *C. elegans* and AD mice, NR prevented the development and progression of Aβ pathology (140-143). In triple transgenic model of AD that causes DNA repair deficiency, NR prevented neuronal damage by phosphorylated tau, neuroinflammation, synaptic dysfunction and cognitive decline (142). NR has been shown to prevent mitochondrial defects, age-related dopaminergic neuronal loss and motor decline in fly models of Parkinson's disease, providing an avenue for neuroprotection in PD and other neurodegenerative diseases (140). As compared to nicotinic acid and nicotinamide, oral administration of NR elevated mouse hepatic NAD^+ with superior pharmacokinetics and in a 52 year old man, a single oral dose of 1000 mg NR increased, by 45.5 fold, the blood levels of nicotinic acid adenine dinucleotide (NAAD) which acts as a NAD^+ biosynthesis intermediate and increased NAD^+ by 2.7-fold (144). Treatment of these cells with NR, induced the mitochondrial unfolded protein response and synthesis of prohibitin proteins, and this rejuvenated these cells in aged mice. NR also improved mitochondrial function and prevented MuSC senescence in the mdx (C57BL/10ScSn-Dmd^{mdx}/J) mouse model of muscular dystrophy and prevented the senescence of neural and melanocyte stem cells and increased the life-span in mice (132). Reductions in NAD^+ in natural aging, which results from mitochondrial dysfunction, has been shown to impair muscle fiber integrity whereas supplementation of the NR has been shown to reverse the progressive muscle dysfunction in mice (145).

In a first clinical trial of pharmacokinetics of NR in humans, single doses of 100, 300 and 1,000 mg of NR, in 12 healthy subjects (ages 30–55 years old) produced dose-dependent increases in the blood NAD^+ metabolome, NAD^+ and NAAD levels, without inducing any adverse effects (145). In a double-blind and placebo-controlled study in 120 healthy adults (60–80 years old), NR (250 mg and 500 mg), did not evoke any toxicity and induced dose-dependent increase of blood NAD^+ levels after 4-weeks and these levels were sustained for the entire eight week duration of the study (146). In a similar double-blind, placebo-controlled study in 55–79 year old healthy subjects, NR administered orally at 500 mg, twice a day was well tolerated and effectively elevated NAD^+ levels, and reduce systolic blood pressure and aortic stiffness (147). These data, therefore, show that age related decline of NAD^+ and the associated age related pathologies can effectively be reversed by the substitution of NAD^+ by administration of NAM, NMN or NR.

AMPK is activated by nutritional restriction and CR as well as by metformin that has long has been used for the treatment of prediabetes and type 2 diabetes, and is currently being considered for the treatment of obesity, for its cancer effects, as an approach for prevention of cognitive impairment, dementia, and Alzheimer's disease as well as an anti-aging medicine (148-153). The adult dose of metformin for the treatment of diabetes is 2 grams (12 mmol) per day from which 6 mmol is excreted daily by the kidneys and the other half is lost in feces (154). Metformin is the most potent member of biguanides and is more effective than buformin and phenformin that appear to act through the mitochondrial complex I (155). Proteomic analysis has revealed that metformin upregulates degradation of branched-chain amino acids, the citrate cycle, glycolysis, and pyruvate metabolism (156). The mode of action of metformin has provided conflicting interpretations. Originally, meformin was suggested to be a "caloric restriction mimetic", acting similar to DR through the AMPK and LKB1, a view that is no longer considered viable (157). Metformin is thought to act similar to a mild uncoupler for ETC, blocking retrograde electron transport and peroxide production. In isolated mitochondria, 25 mM metformin completely inhibited complex I-driven O_2 flux and led to an increased ROS production. Metformin apparently binds to a putative specific carrier in the inner mitochondrial membrane that allows its enrichment from micromolar levels in the cytosol to millimolar levels in the mitochondrial matrix leading to an increase in ADP to ATP ratio (158-159). The phase III multi-site TAME (Targeting Aging with Metformin) trial has proposed metformin as an antiaging drug in model organisms (160-161). In *C. elegans*, fed with live *E. coli* subjected to 25 or 50 mM metformin life-span was increased by 13 to 36% (85). The authors concluded that, the effects of metformin was indirect, due to inhibition of the folate metabolism in the bacteria leading to nutrient deficiency resulting in decreased

availability of methionine and suppressed levels of S-adenosyl methionine (SAM) and decreased SAM/S-adenosyl-L-homocysteine (162-163).

Deletion of *prdx-2* gene, that belongs to a family of peroxidases, the so-called peroxiredoxins (EC1.11.1.15) abolished the effect of metformin on life-extension, and resulted in the death of the treated worms (164). According to others, metformin acts through "lysosomal" pathway and LKB1-AMPK and mTORC1 metabolic signaling networks. Metformin extended health-span as evident by reduced pigmentation and prevented age-related decline in fitness (locomotion body bends) and promoted life extension by activation of the orthologue of AMPK (AAK-2) in *C. elegans*. It is proposed that, metformin actions are directed at lysosomes, since metformin failed to increase life-span in lysosomal mutants (156). It has been suggested that the life-span extension in *C. elegans* by metformin involves AAK-2-dependent translocation of SKN-1 into the nuclei and increased activity of AAK-2 which requires presence of an intact AAK-2/AMPKα subunit and the SKN-1 transcription factor (157). However, meformin failed to extend life-span in the mutants that lacked the orthologues of LKB1 (*par-4*) or axin (*axl-1*) (165). Despite the fact that metformin increased activation of AMPK at 10 mM in the tissues of *D. melanogaster*, it did not extend their life-span (166-167). Also, the life extension by use of 0.1% metformin in male C57BL76 mice has not been reproduced (168-169). However, there are other data that support the notion that metformin extends life in *C. elegans, Drosophila,* rodents and humans, and it can prevent the development of cancer and cardiovascular diseases (149-150, 153, 170-171). Some of the effects of metformin could be mediated through inhibition of mTOR complex-1 function in an AMPK-independent manner via RagGTPase (172).

2.3. Inhibition of mTOR

Rapamycin (Everolimus or Rapamune) is a compound with antifungal, immunosuppressive, and antitumor properties (172-175). Rapamycin acts, in part, by forming a gain of function complex with the peptidyl-prolyl-isomerase, FKBP12, and inhibits signal transduction pathways which are required for cell growth and proliferation (176). However, in 1994, it was realized that the rapamycin-FKBP12 complex directly targets the mTOR (177-179). Pharmacological inhibition of mTOR by rapamycin has confirmed that the role of mTOR is evolutionarily conserved and it acts as a strong regulator of longevity in species as diverse as *S. cerevisiae*, *C. elegans*, *D. melanogaster*, to *Mus musculus* (181-182, 185-294). Administration of rapamycin, starting at 270 days of age, extended the life-span in normal mice by retarding aging, postponing death from cancer, or both and in short-lived mutant strains of mice, rapamycin extended their maximum life-span, nearly, by three-fold (194). The activity of mTOR was increased in hematopoietic stem cells (HSC) in old mice. This included increased in the abundance of the mRNA encoding the CDK inhibitors, p16 (Ink4a), p19 (Arf), and p21(Cip1) as well as a relative decrease in lymphopoiesis; and impaired capacity to reconstitute the hematopoietic system. In old mice, rapamycin increased life-span, restored the self-renewal and hematopoiesis of HSCs, and allowed for an effective vaccination against a lethal challenge with influenza virus. When mTOR was activated in the HSCs in young mice, the phenotypes of HSCs in old mice could be replicated (195). Sesamin, a polyphenolic compound in sesame seeds, has recently been reported to extend the life-span in *C. elegans* (196). Since the effects of seasmin on longevity was abolished by daf-15, which encodes the target of rapamycin (TOR)-binding partner, Raptor, it seems that it does not act through sir-2.1 or AMPK, rather, it signals through the unfolded protein response and mTOR.

2.4. Antioxidants

The free radical theory of aging attributes aging to the oxidative damage, therefore, it follows that the relief from oxidative damage by anti-oxidants should extend life-span (197). There is ample evidence that oxidative damages endured by macromolecules are reversible and such reversal prolongs the life-span. For example, overexpression of the antioxidant enzyme, catalase, significantly increased the life-span of the transgenic mice (198). There is a large number of anti-oxidants such as vitamin C and E, lipoic acid, coenzyme Q, melatonin, resveratrol, curcumin, polyphenols, and synthetic antioxidants including antioxidant nanoparticles.

Among these, vitamin C (ascorbic acid) is a powerful hydrophilic inhibitor of lipid peroxidation and inhibits propagation of free radicals (197). Vitamin E is a hydrophobic anti-oxidant that resides in cell membranes and is present in circulating lipoproteins. Indolepropionamide, is endogenous antioxidant, which reduces ROS, by binding to the rate-limiting component of oxidative phosphorylation in complex I of the respiratory chain (199). The geroprotector, Epitalon a synthetic tetrapeptide (Ala-Glu-Asp-Gly) that is known to have antioxidant activity, showed to increase life-span by 11-16% in *Drosophila melanogaster* (200-203).

The di-peptide, carnosine (beta-alanyl-L-histidine) which is found, by and large, in muscle and brain has a large number of pro-longevity effects (204). Carnosine acts as anti-oxidant and radical scavenger, as a neuroprotector against free radicals, has lipid-peroxidase and anti-inflammatory effects, quenches reactive carbonyl species, inhibits glycation of low-density lipoproteins that promote foam cell formation, has membrane stabilizing action, protects against ischemic damage, prevents telomeric damage and attrition, and has been shown to prevent age related decline in mitochondrial functions, and senescence of fibroblasts (205-216). Carnosine also increased cellular longevity and Hayflick limit and showed rejuvenating effect in human fibroblasts and increased the life-span by 20% in male and not female *Drosophila melanogaster* (216-218). The Trolox- (water-soluble analog of α-tocopherol) acylated derivatives (S,S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carbonyl-β-alanyl-L-histidine (S,S-Trolox-carnosine, STC), increased the life-span by 16% in males and 36% in female fruit flies (219). Carnosine suppressed the adverse effects of age-related disorders that show protein glycoxidation such as Alzheimer's disease and type-2 diabetes (220-225).

The stilbenoid polyphenol, resveratrol (3,5,4′-trihydroxy-trans-stilbene,), was originally isolated from the roots of white hellebore (*Veratrum grandiflorum, O. Loes*) and of *Polygonum cuspidatum.* Resveratrol is present in peanuts, blueberries, pine-nuts, and skin and seeds of red grapes, (or *Fallopia japonica*) (226-228). Resveratrol has been shown to have free radical scavenging and anti-oxidant, anti-inflammatory, anti-microbial, anti-carcinogenic, cardioprotective, neuroprotective, vasorelaxant, and phytoestrogenic effects (228). Resveratrol appears to promote vascular health in aging, yet, when was provided with a high protein diet to old mice, it increased the risk for cardiovascular system (229). Resveratrol has shown neuro-protective effects including decreased cholinergic neurotransmission and by preventing neuronal apoptosis. Resveratrol increased the expression of brain-derived neurotrophic factor, clearance of β-amyloid peptides and led to anti-amyloidogenic cleavage of APP in Alzheimer's disease (230).

There are bioactive compounds that are found in a diverse array of foods including olive oil, fish oil, vegetables, beans, nuts, and fruits. The bioactive polyphenol, curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (diferuloylmethane, CUR), is the main component of the yellow extract from the plant *Curcuma longa* (turmeric), a popular Indian spice (231-232). Curcumin is metabolized into its active metabolite, tetrahydrocurcumin (THC), by a reductase found in the intestinal epithelium that, as compared to other curcuminoids, has a strong antioxidant activity (233). Curcumin has anti-inflammatory properties by virtue of inhibiting activation of the inflammation factor, NFκB, and of the IκB kinase complex (IKK)(234). Curcumin also delays aging by inhibiting mTOR kinase (235-236). Curcumin might also retard aging by its actions on AMPK/UCP2 pathway (237). Curcumin, modulated the expression of age-associated genes, improved health span, and extended life-span in *Drosophila Melanogaster* (238).

Tyrosol which is a main phenol present in extra virgin olive oil has been shown to increase stress resistance and significant extension of life-span in *C. elegans*, possibly by its action on heat shock response (HSF-1) and the insulin pathway (DAF-2 and DAF-16) (239). Fisetin is a caloric restriction mimetic that has been shown to protect rat brain against aging induced oxidative stress, senescence, apoptosis and neurodegeneration (240-243).

Quercetin, present in red kidney beans, caper, radish and onion leads to an increase in

nuclear Nrf2 translocation and reduces Nrf2 ubiquitination (244). Quercetin has been shown to have anti-aging effects, to enhance spatial learning and memory, to protect against cognitive dysfunction, and diabetes (245-248). Epicatechin, is a natural flavonol that exerts its neuroprotective effects via activation of Nrf2/ARE and decreases traumatic brain injury and neuronal degeneration in mice (249). A large array of natural phytochemicals, that are present in fruits and vegetables, have shown promising Nrf2-ARE activating effect. This includes sulforaphane, curcumin, epigallocatechin gallate, allyl sulfides which are organosulfur compounds including diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) present in garlic, resveratrol, lycopene, capsaicin, 3H-1,2-dithiole-3-thione (d3t), 3-O-caffeoyl-1-methylquinic acid, brazilin, cafestol, carnosol, chaocone, and chlorophyllin (250). Omega-3 fatty acids, which are present in fish oil and flaxseed, also increase the nuclear translocation of Nrf2 (251).

There are data that show the damaged molecules might respond to the anti-oxidant treatment. For example, short term administration of N-*tert*-butyl-*α*-phenylnitrone (PBN) to aged gerbils reduced the protein carbonyls in brain, augmented the activity of glutamine synthetase, and normalized, the number of errors in radial arm maze patrolling behavior, to the values that were observed in young animals. However, these changes did not persist when the treatment was stopped (252). Similarly, treatment of old mice (17.5 months) with high-CoQ diet (2.81 mg/g) for 15 weeks led to reduced oxidative damage in proteins and concomitantly improved special performance in Morris water maze test (253).

In Hutchinson-Gilford progeria syndrome (HGPS), Mesenchymal Stem Cells (MSCs) fail to respond or survive the oxidative stress as a result of being able to mount an appropriate NRF2 response (254-259). NRF2-activating compounds such as oltipraz, have been shown to rescue the accelerated attrition of iPSC-derived MSCs in this type of progeria, showing that anti-oxidants are among the arsenals that can effectively be used to defend against oxidative damage in aging (260).

2.5. Hydrogen sulfide

In flies, the longevity benefits of DR can be erased, by adding back the EAA to food (53). Other DR regimens that restrict specific nutrients, including protein or EAAs, without periods of food restriction, also extend life-span and health-span in *Drosophila* to mice (261-263). One of the best examples of such a diet is methionine restriction that shows that this approach can also extend life-span effectively in yeast, worms, flies, rodents, and human cells in culture (163, 264-270). Restriction of cysteine also results in stress resistance, metabolic fitness and it causes 42% increase in mean and 44% increase in maximum life-span (271-275). Thus, restricting diet in sulfur amino acids (SAA) are equally effective in rendering the same impact as DR on longevity and such a diet is easier to be implemented by humans. The beneficial effects of SAA deprivation can be provided by an increase in the supply of the gasotransmitter, H_2S, to the body by consumption of garlic (37). DAS, DADS, and DATS in garlic, effectively release hydrogen sulfide (H_2S) after consumption (276). The allyl iso-thiocyanate, derived from Wasabi, mustard, Arugla and horseradish, which are known to exert many health benefits, are also effective means for increasing the level of H_2S in the body (277). Members of the Brassicaceae or Cruciferae, which are better known as the mustards, the crucifers, or the cabbage family, including arugula (Eruca sativa Mill), produce the iso-thiocyanate, sulforaphane, which has been shown to increase the release of H_2S *in vitro* (278). The sulfide in these cultivars, which is released by cooking, ranges from 0.02 to 0.39 ppm (278-280).

The clear image as how dietary restriction (DR) without malnutrition improves the life-span has emerged recently, and some of the molecular mechanisms that underlie such life extension have come to focus in the past few years (281). There are several lines of evidence that the transsulfuration pathway (TSP) is evolutionary conserved and that the H_2S improves glucose tolerance, increases stress resistance, is cytoprotective and has life extension properties. Hine *et al*, reported in 2015 that in a mouse model of DR-mediated stress resistance,

the restriction of SAA, cysteine and methionine, increased expression of the enzyme cystathionine γ-lyase (CGL, CTH or CSE) of the transsulfuration pathway (TSP), which increased H_2S production and protection from hepatic ischemia reperfusion injury (282-284). The positive impact of DR on stress resistance and on H_2S production was shown to be extinguished by SAA supplementation, mTORC1 activation, and chemical or genetic CGL inhibition. It has been shown that the TSP-dependent H_2S production is conserved in yeast, worm, fruit fly, and rodent models of DR-mediated longevity. Together, such findings have shown that H_2S production is essential to the positive effects of dietary restriction and that the impact of such a diet, at least in part, is due to the restriction of consumption of cysteine and methionine which, in turn, increases the production of H_2S.

The production of H_2S diminishes with age and thus, the protective effect of this gas gradually declines as the organism grows older. For example, it has been shown that there is an age-related decline in CGL and CBS expression and H_2S production in various tissues in rats. It has been shown that such a reduction can be prevented, by a long-term 10–40% CR, when instituted from 8 to 38 months of age (285). Short-term SAA restriction even for 1 week, has shown to increase hepatic CGL expression while a 5 week restriction of SAA has resulted in the elevated expression of hepatic CGL and CBS (286). 20–40% CR has led to a dose-dependent increase in hepatic H_2S production in mice and such an increase has been associated with an improved health, yet, not always it has led to an extended longevity (287-288). The reversal of age related decline in CGL and CBS expression and H_2S production in kidney has been shown in rats to be achievable by 30% CR (289). There is also a strong evidence that H_2S is involved in aging and its normal function is necessary for inhibiting free-radical reactions, activation of SIRT1, and probably by interacting with the age-related gene Klotho (290). H_2S has been shown to maintain the Klotho expression following acute kidney injury. The actions of H_2S are similar to, Klotho, which induces expression of manganese superoxide dismutase (SOD) and resistance to oxidative stress, by activating the forkhead transcription factors (FOXO) (291-292).

2.6. Senotherapeutics, senolytics, senomorphics and anti-inflammaging strategies

One of the prominent hallmarks of aging is the development of cellular senescence which occurs in aging tissues and contributes to the tissue or organismal aging, and to the diverse Age-Related Diseases (ARDs). Genetic ablation of senescent cells increases health-span and reduces the risk of age-related pathologies in mice. Thus, senotherapeutics is a new strategy for the removal of these cells as a fight against aging. Senotherapeutics include senolytics which selectively kill senescent cells and senomorphics which delay the progression of young cells to senescent cells in tissues, restore the functions of these cells to the levels found in young cells, or clear the senescent cells from tissues by immune-system mediators. Among these, rapamycin, which acts as an mTOR inhibitor, increased the median and maximal life-span of both male and female mice when was administered beginning at 600 days of age (293). Administration of rapamycin to mice, beginning at 270 days of age, also increased survival in both males and females. The pattern of the development of the disease, however, did not differ in rapamycin-treated mice as compared to those of control mice. There is further evidence that rapamycin, along with increasing the life-span, also increases the function of various stem cells (294-298). Aging is associated with an increase in mTOR activation in stem cells and progenitors of the hematopoietic system (296). Administration of rapamycin to old mice protected against the age-dependent decrease in the function and of increase of biomarkers of aging in hematopoietic stem cells. The life extension property of rapamycin could be attributed to the postponement of death from cancer, by slowing aging, or both. The effect of the rapamycin also appears to involve epigenetic reprogramming by prevention of loss of several histone marks that decrease with age namely, H3R2me2, H3K27me3, H3K79me3, and H4K20me2 (299). These data show a distinct role for mTOR signaling in the regulation of mammalian life-span, and that pharmacological extension of life-span in both sexes is possible by targeting the mTOR pathway.

The senescent cells cause a host of age related complications, namely production of ROS, inducing by-stander senescence in other cells, causing senescence-associated mitochondrial dysfunction (SAMD), release of inflammatory cytokines, the so-called Senescence-Associated Secretory Phenotype (SASP), and impairing immune surveillance (303). Consistent with the by-stander effect, transplanting a relatively small number of senescent cells into young mice, led to the spread of cellular senescence in host tissues and persistent physical dysfunction (304). Transplantation of even fewer senescent cells to old mice shortened health-span and life-span and reduced their survival (304). Although, normally, the senescent cells are removed from tissues, aging leads to impaired clearance of these cells and their progressive accumulation in aged tissues, in different species including rodents, primates and humans (305-309). Consistent with adverse effects of such cells in tissues, the inducible clearance of p16INK4a-positive senescent cells has been shown to delay natural and premature aging in mice (310-315). Thus, a new therapeutic regimen for aging is to effectively remove senescent cells from tissues or to reduce the impact of their SASP (316-319).

The first intervention involving use of senolytics used dasatinib, a protein tyrosine kinase inhibitor, and the plant flavonoid, quercetin (320). The activity of these two drugs was different. Dasatinib removed senescent human preadipocytes whereas quercetin was more effective against senescent human endothelial cells and mouse bone marrow-derived mesenchymal stem cells (BM-MSCs). The combination of both drugs, reduced the senescent cells and age related pathologies and increased health-span in chronologically aged mice, in mice that were exposed to radiation, as well as Ercc1$^{-/\Delta}$-progeroid mice. The combined administration of dasatinib and quercetin reduced age related pathologies including Alzheimer's disease, atherosclerosis, hepatic steatosis, osteoporosis, pulmonary fibrosis and cardiac aging (321-324). Other classes of senolytics include inhibitors of kinase pathways such as P13L/AKT (Fisetin), those that bind p53, impact several pathways (Piperlongumine, Quercetin-3-D-galactos), inhibit Bcl-2 (ABT-263, ABT-737, A1331852, A1155463), heat shock protein 90 (17-AAG Geldanamycin), or histone deacetylase (HDAC) (Panobinostat) and UBX0101 which acts as histone deacetylase (HDAC) inhibitor and targets MDM2/p53 and a modified FOXO4-DRI interfering peptide that targets p53/p21 and serpine (316, 325-326). Senolytics have shown a great promise in restoring lost functions in aging tissues. Acute or intermittent treatment of old and progeroid mice with the senolytic agent, fisetin, also has reduced senescence markers in multiple tissues, reduced age-related pathologies, and extended median and maximum life-span (325). The use of dasatinib plus quercetin as a senolytic cocktail, has led to the increase and selective clearance of senescent cells, and reduced secretion of proinflammatory cytokines in explants of human adipose tissue (304). Moreover, intermittent oral administration of senolytics to naturally aged mice and young mice that received senescent cells prevented loss of physical functions and increased survival by 36% and reduced their mortality hazard by 65% (304). Removal of senescent cells has also been shown to reduce age-associated phenotypes and to rejuvenate HSCs (310-314).

Given that senescent cells participate in normal physiology such as wound healing, placental function and embryo development, these cells are normally cleared from tissues by the immune cells. However, immunoscenecence reduces the efficiency of the immune mediated clearance by NK cells, CD4^{+} T cells and macrophages that identify the senescent cells by different targets that appear on the cell surface of these cells. This includes MICA, and ULBP2 expressed by replicatively, oncogene and DNA damaged induced senescent fibroblasts, dipeptidyl peptidase 4 (DPP4), NKG2D ligands and CD9 that is expressed in replicatively and doxorubricin induced human umbilical cord endothelial cells (HUVEC) and human dermal fibroblasts (327-331). The DPP4, which appears on the cell membrane of senescent fibroblasts, is considered to be targetable by the antibody-mediated NK cell-mediated cytotoxicity (332). Another approach is the administration of T cells that, by the expression of the NKG2D chimeric antigen receptor (CAR), can recognize NKG2D ligands on the surface of senescent cells (327).

Senomorphics do not lead to the apoptosis of senescent cells, rather, they reverse the senescent phenotype and oppose the senoinflammation and inflammaging. This includes a wide range of approaches and drugs that include CR, CR mimetics (CRM), antioxidants, anti-inflammatory agents, as well as activators of telomerase, sirtuin, autophagy and proteasome (328-337). The target for the therapeutics varies and include IKK/NFκB pathway (NBD peptide), JAK (Janus kinase) pathway (ruxolitinib), PDGF/FGF pathway (ESC-CM), TGFBR2/p21 pathway (Mmu-miR-291a-3p), ATM kinase (KU-60019), Progerin/lamin A/C (JH4) as well as a number of other drugs with unknown targets (Juglanin, Quercetin-3-O-β-D-glucuronide, (−)-Loliolide, Quercetagetin 3,4′-dimethyl ether) (316). The best approach to the suppression of age related inflammation is to adopt preventive measures which include those that retard the aging process namely, CR, DR, restraining the consumption of protein, and sulfur containing amino acids, metformin, resveratrol, NAD^+, NMN, NR, epimedium total flavonoids, and icariin. It is recommended that the diet be supplemented with zinc (Zn) which often times is low in the elderly. Zn is thought to modulate the immune-inflammatory response and to interact with inflammatory cytokines including interluekin (IL)-6, tumor necrsis factor (TNF)-□ as well as heat shock protein 70 (HSP70)(338-340). It has been shown that individuals that are over 60, if treated with TNF antibody, are less prone to infections (341).

The anti-inflammaging response that the aging organism mounts to counter the inflammaging leads to an increase in the circulating level of cortisol with un-avaoidable consequences including gluconeogenesis, global immunosuppression, frailty induced by catabolic effects, muscle protein catabolism and wasting and bone resorption and osteoporosis (342). Dehydroepiandrosterone (DHEA) and its sulphated precursor, DHEA sulphate (DHEAS), which are secreted by ACTH driven production from adrenal glands and to less extent by the ovary and testis, oppose the negative effect of cortisol induced by the anti-inflammaging response. These hormones antagonize the effect of cortisol at the glucocorticoid receptor level, directly by suppressing their production or by virtue of downstream metabolites and by opposing the cortisol induced immunosuppression (343-344). The ovarian and testicular DHEA are converted to the estrogen and testosterone and, for this reason, can not contribute significantly to this response (345). Unfortunately, the levels of these beneficial hormones reach a peak in early adulthood and then decline sharply with age so that by age 70 they reach to 10-20% of their values in youthful individuals (346). Whereas, high cortisol levels are associated with increased death in patients who suffer stroke, heart failure, sepsis, and sarcopenia, the low concentrations of DHEAS are associated with diverse age related pathologies including cardiovascular disease, sarcopenia, osteoporosis and mortality (347-353).

2.7. Reactivation of telomerase

There are findings that show that shortening of the telomeres has a significant adverse impact on the life-span of replicatively active cells and that reversal of telomere shortening can extend the life-span. Age dependent loss of the telomere function, leads to p53 activation resulting in loss of tissue stem cell and progenitor functions, apoptosis, impaired proliferation and senescence, marked tissue atrophy and physiological impairment in many organ systems (354). The production of transiently or reversibly immortalized engineered cells with active telomerase that do not harbor oncogenic mutations appears to be safe and offers the possibility of treating a variety of chronic diseases and age related pathologies that emerge from telomere based replicative senescence. The expression of the catalytic subunit of human telomerase (hTERT), which restores telomerase activity has been shown to reduce senescence and to extend the life-span of many human cell types (355-361). The hTERT immortalized cells have a normal karyotype and normal functions such as normal cell cycle controls and functional p53, p21Cip1, and p16Ink4a/pRB checkpoints, and like normal cells are contact inhibited, and require growth factors for proliferation (362).

Telomerase deficient mice have been used to show the relationship of the decline of telomeres, mitochondria and stem cells during aging (363). Loss of telomeres and their un-capping leads to impaired

responses to tissue injury, progressive tissue atrophy, stem cell depletion, and ultimately to multi-system organ failure (363). A knock-in allele that encodes a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-Estrogen Receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter was used to examine the effect of reactivation of telomerase activity on halting or reversing the impacts of deficiency in telomerase activity. Reactivation of telomerase, extended telomeres, reduced DNA damage signaling, led to the proliferation of quiescent cells, and erased degenerative phenotypes in testes, spleens and intestines (364). The reactivation of telomerase in adult tissue stem cells that suffered from shortened telomeres reversed degenerative pathologies that were reminiscent of age related pathologies in multiple organs (364). This rejuvenating intervention does not appear to be associated with the loss of differentiated phenotypes.

By overexpressing HRP-1, a telomere-binding protein, the telomeric length was extended in *C. elegans* and these animals were shown to live longer. Moreover, the extension of life-span in these animals was due to the increased telomere length, and not due to the overexpression of HRP-1 (365). Inhibition of proliferation in the virus-transformed human fibroblasts, could be overcome by the ectopic expression of the wild-type reverse transcriptase protein (hTERT) of human telomerase (366). It was shown that the activity of reverse transcriptase of telomerase synergized with calorie restriction and extended health-span and life-span in mice (367). Telomerase was also shown to prevent the accelerated cell aging that occurs in fibroblasts of patients with Werner syndrome (368). Ideally, stem cells can be transiently forced to express hTERT until such time that the telomeres are sufficiently elongated, and, then, the rejuvenated cells can be returned to the aged individual to restore functions that are lost due to aging in stem cells. Clearly, before such a practice can enter the clinical arena, the efficacy, long term safety and the assessment of its oncogenic potential are required (369).

2.8. Prevention of stem cell exhaustion

A predominant feature of aging is a progressive decline in stem cell function that results from cumulative epigenetic alterations that ultimately halt tissue repair (370). Like other cells, human adult stem cells, are subject to telomere shortening, and the diverse epigenetic modifications that are involved in aging including global loss of H3K9me3, and changes in the nucleolus organizer region related to ribosomal DNA (NOR-rDNA) (371-378). The multi-potent progenitor cells from adipose tissue show age-dependent loss of self-renewal capacity and exhibit an increased tendency to undergo adipogenesis (379). Bone-marrow-derived mesenchymal stem cells (MSCs) of patients with Hutchinson–Gilford progeria syndrome, are defective in their ability to differentiate (380). Similarly, the MSCs show loss of proliferation and differentiation potential, increase in senescence and loss of capacity to differentiated in aged animals (381-383). In many model organisms, the senescence and exhaustion of stem cells have been shown to be due to dysregulation of metabolic and nutrient-sensing pathways. Among these, decreased serum levels of insulin growth factor (IGF)-1 appears to promote stem cell quiescence, whereas, maintenance of these systems promotes proliferation of adult stem cells.. For example, repletion of NAD^+ in stem cells, improved mitochondrial and stem cell functions and enhanced life-span in mice (384). Moreover, introducing germ-line stem cells to *C. elegans* extended their life-span and implantation of neural stem cells extended life-span in Niemann-Pick C1 mice (385-386). Thus, it is clear that approaches that are designed to prevent age related decline in aging, such as prevention of exhaustion of stem cell pool, are one of the ways to extend human life-span.

Notably, overexpression of the enzymatic subunit of telomerase, TERT, in mice, on a cancer-resistant background or late in life, increased median life-span, suggesting that the length of telomeres and life-span are intimately linked (387-388). The self-renewal, and regenerative potential of HSCs are maintained by fasting and CR through modulation of the signaling through IGF1-PKA, mTORC1 and SIRT1 pathways and DR has been used to effectively rejuvenate the activity of muscle and intestinal stem cells (389-390). It has been shown that the life can be extended in progeroid mice and degenerative phenotypes can be prevented by the transfer of muscle-derived stem cells (MuSC) from young mice

(391). In a mouse model of progeria, muscle-derived stem/progenitor cells (MDSPCs) were defective in proliferation and multi-lineage differentiation. The intraperitoneal administration of MDSPCs from young wild-type mice, to progeroid mice restored proliferation and differentiation defects of aged MDSPCs and led to a significant rescue from degenerative changes and vascularization defects in tissues and increased in health-span and life-span. The rejuvenating effect of the stem cells from healthy young animals appears to be due to secretion of soluble factors. For example, systemic factors from young mice have been used to rescue the dysfunction of neural and muscle stem cells in old mice (392-393).

Three chemicals which are all known activators of the nuclear factor erythroid 2-related factor (NRF2) pathway, metformin, resveratrol and Oltipraz, stimulated the proliferation of pre-senescent hMSCs in the WS that induces progeria (394). By increasing the interaction between SIRT1 and Lamin A, resveratrol has shown promising effects by opposing the decline in the adult stems and to increase life-span in mice with premature aging (395). To create stem cells with better quality, a single-nucleotide variation (A245G) was introduced in the NRF2 locus. This change improved NRF2 stabilization and transcriptional activation of its target genes, conferred resistance to neoplastic transformation, delayed cellular senescence, and led to the self-renewal activity, and a better regenerative ability of stem cells *in vivo* (396). By induced expression of NRF2 target genes, the FDA approved, oltipraz, has shown to reduce the accelerated exhaustion of iPSC-derived MSCs in HGPS (260). Similarly, by activating sirtuins, the NR which was shown to delay the induction of senescence in MuSCs and aging in adult stem cells, also has shown to extend life-span in mice (132). The beneficial effects of metformin on aging, by activating AMPK which has been shown in worms and mice, is currently being carried out in humans (7, 157, 377, 397). Vitamin C, which acts both as a redox regulator and an epigenetic modulator, and reduces ROS levels and loss of function, has been shown to increase proliferation of MSCs in a stem cell model of Werner syndrome (398-400).

3. REJUVENATION STRATEGIES

There are several approaches that can restore lost functions in aged cells and lead to the rejuvenation of tissues without the need to repress differentiation and generation of a pluripotent state. Moreover, there are now new evidence that the aging clock can be reset to an earlier time point by several strategies such a partial reprogramming, or by use of a drug cocktail comprised of metformin, GH and DHEA. We will examine the available models that supports the notion that aging reversal is feasible.

3.1. Resetting of the aging clock and reversal of aging

Gene expression, which is requisite to life and all facets of cellular functions, is controlled by the structure of chromatin and by the state of the epigenome (401-402). The epigenetic landscape and retention of older “immortal” strands and segregation of the new strands to the daughter cells, is known to be important to the cell fate, and differentiation decisions of stem cells (403). This raises the possibility that the state of chromatin and epigenome might also underlie, some if not all, aspects of aging. One of the best characterized epigenetic means for regulation of gene expression occurs by the methylation of the DNA that remains stable or even can be passed on to the next generation until such time, that based on the cellular needs, this state is modified by the demethylation processes. Based on analysis of 8,000 samples from 82 Illumina DNA methylation array datasets, that included 51 healthy tissues and cell types, Horvath *et al* showed that the DNA methylation status of 353 genes can predictably and accurately estimate the age of any tissue within a narrow 2 year margin (404-406). The possibility that, these methylation sites are not merely markers of aging but also cause aging, is a possibility that has not yet been ruled out. This DNA methylation age or Horvath or epigenetic clock has some inherent properties including being zero in embryonic and induced pluripotent cells (iPs). The epigenetic clock shows sequential changes with the passage number of *in vitro* cultured cells. Interestingly, the clock was a great predictor of heritable acceleration of age and could even be applied to the determination of the biologic age of tissues from chimpanzees.

Thus, it follows that measures that can reset the aging or epigenetic clock and even to set it to zero now can be reliably tested. Among such measures, nature itself has provided us with many clues and circumstances that suggest that the aging clock can be reset to an earlier time-point. However, opportunities that reset the aging clock to zero must be approached with a great caution since they may unleash the possibility that pre-existing DNA mutations may lead to carcinogenesis. Among such conditions are parabiosis, genetic reprogramming, forced induction of near stemness by periodic introduction of pluripotency genes, fertilization, somatic cell nuclear transfer (SCNT), young extracellular matrix, and blood factors such as growth and differentiation factor (GDF))11.

Since aging results in progressive increase in the cortisol/DHEAS ratio, one approach is to provide DHEA or DHEAS as a supplement, and conclusive trial data that such an approach is beneficial is just emerging (343, 408-410). Recently, a trial was carried out and the participants, initially, received for a week, recombinant growth hormone (hGH alone) (0.015 mg/kg/day) and then 50 mg/day DHEA in the second week and finally, these were administered with 500 mg/day metformin in the third week. At the fourth week, all doses were individualized based on particular response of each participant (411). This treatment led to the improved immunological response and risk indices and reversed the aging clock. The rate of reversal of the epigenetic aging relative to the actual chronological age accelerated from −1.6 year/year from 0–9 months to −6.5 year/year from 9–12 months. The GrimAge predictor of human morbidity and mortality persisted six months after the treatment was discontinued. This is the first report that the epigenetic age estimator of life-span can be reversed by an anti-aging strategy.

This study clearly points to the fact that aging is not fixed and similar to differentiation can be reset and that strategies that successfully rewind the clock likely resume normal function of organs, tissues and cells, and bear the potential to allow the stem cells to regain their regenerative potential with the hope to reverse age related organ and tissue declines and pathologies. There are natural circumstances such as fertilization that are consistent with the idea that nature has found ways to reset the aging clock to zero or preferably just to an earlier time-point consistent with the youthful state of embryos to young adults. Moreover, the rejuvenation can be achieved by epigenetic reprogramming that involves somatic cell nuclear transfer (SCNT) or generation of induced pluripotent cells (iPs). Other approaches include partial or episodic reprogramming, heterochronic parabiosis, or exposure of aged cells to a youthfull extracellular matrix. The only caveat is that aging is associated with the accumulation of mutations in nDNA and mDNA that are not be remedied by rejuvenation strategies, requiring development of personalized medicine by sequential and partial rejuvenation of tissues in a step-wise fashion or by removing the unwanted mutations by clustered regularly interspaced short palindromic repeats (CRISPR). Also, we, so far, lack knowledge on sustainability and endurance of the available strategies, requiring the understanding that how often such rejuvenating regimens must be re-introduced.

3.2. Fertilization and somatic cell nuclear transfer (SCNT)

Epigenetic changes are indispensable to life and represent reversible processes by which response to environmental and developmental cues are received, leading to alterations of the DNA and histones by a host of enzymes such as methyltransferases, demethylases, acetyltrans-ferases, and deacetylases (412-414). Many enzymes, that modify chromatin, lack intrinsic DNA binding specificity and require special docking sites on chromatin, or are actively recruited by long and short noncoding RNAs or sequence-specific transcription factors (415-418). The so-called "*cis*-epigenetics" lead to transcription of genes that determine the cell fate and lock cells in a differentiated state (416). The gene expression is controlled by the extent of cytosine methylation of the regulatory regions of the genes, with heavy methylation, oftentimes, leading to repression of gene expression. These changes also include the modifications in chromatin state induced by methylation or acetylation of histones that can turn on (histone acetylation or histone 3 trimethylated at

lysine 4; H3K4me3) or turn off (histone 3 trimethylated at lysine 27;H3K27me3) the transcriptional activity of genes on demand (412, 419). The regulation of gene expression may also be achieved by a host of RNAs and proteins such as transcription factors, the so-called "*trans*-epigenetics" (416, 420). The epigenetic changes are normally stable and not prone to change by environmental cues, a process referred to as "canalization" (421). Despite being stable, the epigenetic modifications are not hard-wired and can be passively modified, for example, by sequential cell divisions that can be reinforced by specific enzymes that endow cells with a new epigenetic state (412, 422). DNA methylation changes occur and correlate well with the age of tissues. In fact, the DNA methylation status of some loci in any tissue including blood has been found to be sufficient to accurately assess the biologic age of the tissue and serve as a better predictor of the mortality than any other risk factor (404, 423-424).

The available data suggest that epigenetic changes that drive the aging processes can reliably be reset via extensive epigenetic remodeling that starts at fertilization and continues during germline specification and early development. Early development is associated with two major waves of epigenetic reprogramming, one that occurs at fertilization and, the other, later during germ cell development and imprinting (425). Fertilization acts as s potent mechanism for resetting of the aging clock by "reprogramming," of the zygotic nucleus by the factors that reside within the egg cytoplasm. In humans, this process is initiated immediately after fertilization and at the moment that the sperm head enters the ooplasm. After fertilization, the genome undergoes epigenetic reprogramming that entails genome wide modifications of 5-methylcytosine and DNA repair (425-426). The resetting of all age related changes in ovum is required to allow for resetting of the epigenetic landscape that gives rise to another organism with a normal life-span. The zygotic genomic reprogramming is unique since it entails the formation of so-called bivalent domains that include both H3K4me3 (active) and H3K27me3 (repressive) marks that remain on standby until activated (427). Chromatin marks are not spared from changes that typically occur in the enhancer elements marked by histone H3 monomethylated on lysine 4 (H3K4me1). This state correlates well with increased levels of chromatin interactions, whereas loss of this histone modification, leads to reduced levels of chromatin interactions (428). These enhancers get activated during differentiation of embryonic stem cells by virtue of modification of histone H3 lysine 27 from trimethylation (H3K27me3) state to an acetylated (H3K27ac) format (429-430). Although the rate of aging in germ cells and their biologic age might differ from the changes that occur in somatic cells, germ cells are not immune from cellular and molecular assaults of aging (431-432). Early during the development, with the notable exception of imprinted loci, primordial germ cells also reset the methylation marks of their genome, reaching a state of global hypomethylation that is stably retained. Methylation levels reach to their lowest levels in the developing embryo before gastrulation (433).

The notion that egg cytoplasm has rejuvenating effect, was a prelude to the concept to achieve cloning by somatic cell nuclear transfer (SCNT). This process involves removal of the nucleus of a differentiated somatic cell and its transfer to the cytoplasm of an enucleated oocyte (434-435). The first successful attempt was carried out by the introduction of nuclei from cells of blastula to the enucleated cells of a frog. The rationale for this choice was that it was known that all the nuclei of the blastula were equivalent. These early experiments clearly showed that nuclear transplants into eggs can give rise to normal embryos. Later, it was shown that egg transplantation of nuclei of endoderm cells of *Xenopus laevis* could give rise to swimming tadpoles that appeared to be entirely normal and at least 30% of nuclei of the blastula and at least 4% of gut-cell nuclei from hatched tadpoles contained all the required genetic information for the formation and functioning of a normal adult organisms (436-438). However, frogs which were derived from the nuclei of differentiating cells, exhibited more abnormality than those which were derived from embryonic cells. For example, 7 out of 27 frogs that were derived by the transfer of the nuclei of the gut cells of the hatched tadpoles were sterile. Although, initially, the offsprings were derived from SNCT of nuclei of early embryos, or embryo-derived cells during primary culture, ultimately, SCNT was successfully carried out by transplanting the nuclei from the mammary

glands of a sheep to an enucleated egg. These early attempts, ultimately, gave rise in 1996, to the birth of the first mammalian cloned animal, the Dolly (439). Dolly was fertile and gave rise to triplets, Lucy, Darcy and Cotton in the year 2000. At the age of 4, Dolly developed arthritis and was euthanized due to the development of disabling arthritis and lung carcinoma. However, this landmark achievement led to an entire field of cloning and provided the proof of hypothesis that the state of the DNA or epigenome of an adult cell is not a barrier to the generation of a normal adult and that nuclei of differentiated somatic cells can successfully revert to a totipotent state. Given that most cloned animals die, it is clear that the resetting of the aging clock and epigenetic reprogramming do not fully replicate the reprogramming that occurs in fertilized eggs (440).

These early studies clearly showed that the nuclei of aged differentiated cells can successfully give rise to embryos that become fertile adults and that the aging within such nuclei is not a hindrance to the reprogramming and resetting of the DNA, to a more youthful state, once placed within the rejuvenating environment of the ooplasm. Despite the fact that the age related changes and pathologies accumulate through a life-time, they are not passed to new generations. Each life begins with both the chronological and biological age being re-wound and set to zero and, moreover, there is evidence that longevity can be inherited and even be imprinted (441). Thus, reversal, or “resetting to zero,” of the aging clock appears to be deeply embedded in the nature of life.

3.3. iPSC and epigenetic reprogramming

As stated, the epigenetic marks, for example, the DNA methylations, are often very stable and not subject to change and reprogramming (442-443). Yet, the cell fate has been shown to be reversible through trans-differentiation or by SCNT. The epigenetic changes were also achieved, merely after 2 days, by the conversion of lymphocytes to muscle fibers by formation of heterokaryons of B lymphocytes and C2C12 myotubes (444-445). This conversion required the extinction of the lineage-specific lymphocyte associated gene repertoire by histone deacetylase (HDAC) activity and establishment of expression of muscle specific genes. Interestingly, the fusion of fibroblasts with human embryonic stem cells (hES) created tetraploid cells that exhibited the morphology, growth pattern and molecular signature of hES cells. Moreover, in ES cell hybrids, differentiation was extinguishedm, and, stemness rewired the cell fate, towards the stem cell programs and pluripotency (446-447). One possible explanation for this overriding effect of the somatic cell differentiation programs, lies in the *trans*-epigenetic enforcement that establishes a strong foothold on the maintenance of the ESC state by virtue of the fact that, the transcription factors that convey stemness, co-occupy not only their own enhancer elements but also the enhancers of other members. These pluripotency factors also bind and activate and suppress set of genes which are essential to the pluripotent state. For example, recent evidence has coupled the expression of Xist and the in-activation of X-chromosome to the expression of pluripotency. To achieve gene dosage parity between the sexes, the long non-coding expression of Xist mRNA is required for transcriptional silencing of one of the two X chromosomes in female cells. Oct4 (Pou5f1), Nanog and Sox2 are shown to lie at the top of the XCI hierarchy, and to regulate XCI by triggering X-chromosome pairing and counting. Thus, it becomes evident that that, genetic factors that underlie pluripotency, jointly repress Xist and couple X inactivation reprogramming to the control of pluripotency during embryogenesis (448-449).

The early work by forming heterokaryons, led to the landmark work of Shinya Yamanaka who demonstrated that differentiation is not fixed and can be reversed by generation of cells that are pluripotent (iPS) by introduction of merely four transcription factors, Oct4, Sox2, Klf4, and cMyc (OSKM), that reset the differentiation programs (450). Such dramatic reversal suggests that developmentally established epigenetic marks as well as epigenetic landscape of aging cells can all be erased and reversed. This is evident by rejuvenation of chromatin state of cyclin-dependent kinase inhibitor, p16 (*CDKN2A*) locus, which is progressively expressed with age, and causes the cell cycle arrest and senescence (426, 451). The idea that the aging clock is reset to zero in iPs cells became evident when it was shown that these cells can give rise to germline

cells as well as embryos (453). These studies showed that the global gene expression as well as chromatin states of iPs cells are remarkably similar to those in embryonic stem cells (ESC) and that indeed the resetting of the aging clock is feasible merely by introduction of Oct4, Sox2, cMyc and Klf4 transcription factors in the terminally differentiated cells (454). Many of these epigenetic changes that occur during the formation of iPs cells are remarkably similar to those which occur in the early zygote (455). Thus, it follows that transit of somatic cells to pluripotency, not only extinguishes the differentiated state and render these cells pluripotent, it allows these cells to be differentiated to other cells such as hematopoietic stem cells (HSCs) or neural stem cells (NSCs) that are rejuvenated (456). In contradistinction, direct conversion of fibroblasts to NSCs failed to reverse aging in the modified cells (457).

The un-winding of the aging clock, has provided the unique opportunity to consider that, by introduction of iPs, produced from any aging individual to the same person, tissues can be generated that are more youthful, and provide the unique opportunity to potentially extend their lives. However, such an initial enthusiasm was tempered by the fact that the iPs cells lead to the formation of teratomas, a side-effect that appears to be due to the tumorigenic effect of cMyc (458). This led to the consideration to eliminate cMyc from the reprogramming cocktail and to induce reprogramming with merely three transcription factors Oct4, Sox2, and Klf4 (459). Senescent cells from centenarians or cells derived from patients with HGPS have successfully been reprogrammed and the reprogramming has led to an increase in telomeric length, and a more youthful gene expression profile, and reduced oxidative stress (257, 259-260). Restoration of fibroblasts of patients with HGPS also lends further support that, reprogramming, dramatically improves cellular functions (261-265). However, there are considerations that appear to be obstacles to the clinical usefulness of this approach. This includes heterogeneity and in-efficiency (<1–2%) of this process, likely due to the potency of p16 and p53 that act as barriers to the formation of iPs. Moreover, the time consuming aspect of generation of iPs is a hindrance for introducing the idea as a clinical treatment for the reversal of aging (445, 452, 466). Moreover, the iPs generation may not restore the length of the telomeres nor full telomerase activity (467-468). Thus, before such technologies become therapeutically feasible, there is a need to fully understand how to improve the process, so that the reprogrammed cells become more equivalent to youthful cells and to insure that such cells are not the harbinger of tumorigenicity. The rejuvenation through iPs, perhaps can be substituted by other means that do not require the differentiated cells to fully relinquish their fate by forcing a mere partial or episodic reprogramming or through inhibition of the main culprits of aging programs such as by inhibiting the NFκB or mTOR, by inducing conditions similar to heterochronic parabiosis or by virtue of endowing youth through signaling from young extracellular matrices.

3.4. Partial reprogramming

To avoid the undesirable effects of full reprogramming, and more importantly, to avoid its tumorigenic potential, and yet to realize its beneficial impacts, an alternative approach for reversing age related pathologies has emerged. Given that reversal of age-associated cellular phenotypes has already been achieved *in vitro* by cellular reprogramming, some have resorted to the partial programming using the Yamanaka (OSKM) factors (460, 464-472). Ocampo *et al,* showed the effectiveness of partial reprogramming using a mouse model of premature aging (473-475). The premature aging (progeria), in this model, is due to a G609G mutation in the *Lmna* (LAKI) gene that leads to the accumulation of a faulty truncated form of lamin A (progerin) that disturbs the architecture of nuclear envelope and is also the cause of the human HGPS (476-477). These, so-called LAKI mice, show progeria along with weight loss and age associated damages in many organs. The partial reprogramming was achieved by the cyclic doxycycline responsive *in vivo* induction of OSKM factors and such induction led to the reversal of the aged cell phenotypes and alleviated pancreatic and muscle damages. The partial reprogramming failed to induce the pluripotency marker, Nanog, even after 12 days, suggesting that the reprogramming was not complete. Despite this, there was

remarkable reversal of age related damage including reduction of p53 binding protein 1 (53BP1), which participates in the DNA damage response as well as downregulation of the expression of p53 mediated age-related stress response genes, namely, p16INK4a, p21CIP1, Atf3, and Gadd45B, as well as the senescence-associated metalloprotease, MMP13 and interleukin-6. The partial reprogramming successfully restored the levels of H3K9me3 and H4K20me3 which drop with aging and significantly improved the architecture of nuclear envelope. Besides such changes at cellular and molecular levels, there were improvements in external appearance of these mice such as reduced spine curvature (kyphosis), and restoration of histologic appearance of tissues of major organs, thickening of skin, reduced involution of the white pulp within spleen and lymphoid tissues, decrease in tubular atrophy within kidneys and a significant increase in the median or maximal life-span. More importantly, these reversal of aging phenotypes were not associated with tumor formation nor were permanent, and, within 4-8 days, they were reversible as evidenced by the return of the H3K9me3 modification, and recurrence of nuclear envelope abnormalities. Together, such changes provided the proof of the hypothesis that short term induction of the reprogramming is sufficiently robust to reverse the age related damages that are evident at the tissue, cellular and molecular levels.

One drawback of this initial study was that premature aging model does not faithfully replicate natural aging. For this reason, a non-integrative reprogramming protocol was carried out on tissues from aged mice as well as aged human cells (478). The cocktail was comprised of mRNAs expressed from OCT4, SOX2, KLF4, c-MYC, LIN28, and NANOG (OSKMLN). Reprogramming factors were only transiently applied and then stopped (before the so-called Point of No Return, or PNR). Transcriptomic profiles, indeed, verified that the cell identities were retained after treatment. The epigenetic repressive mark H3K9me3, the heterochromatin-associated protein, HP1**γ**, and the nuclear lamina support protein, LAP2α, showed a decrease in the nuclei of aged fibroblasts and endothelial cells. The formation of autophagosomes, and chymotrypsin-like proteasomal activity, telomere's length, mitochondrial membrane potential and SIRT1 protein levels were increased while the ROS production, the senescence associated beta galactosidase and SASP phenotypes were decreased. Most notably, transient expression of OSKMLN led to the reversal of the epigenetic clock of human somatic cells, including endothelial cells and fibroblasts indicating that methylation age was reversed, respectively, by 1.62 years and 1.07 years. Chondrocytes derived from cartilage of six, 60–70-year-old patients, who suffered advanced stage of osteoarthritis as well as chondrocytes from young individuals were treated with the OSKMLN cocktail. This, treatment did not change the cellular identity of these cells as evidenced by expression level of SOX9, a transcription factor that defines the chondrocytic identity and function and significantly increased the expression of cartilage specific, COL2A1. Whereas, the RNA levels of antioxidant, SOD2, and ATP levels increased, this treatment led to a significant reduction of intracellular mRNA levels of RANKL and iNOS2, as well as in the levels of inflammatory factors secreted by these cells. Transient reprogramming of mouse-derived skeletal muscle stem cells (MuSCs), reduced the time of first division that became similar to the time required for the activation of quiescent young MuSCs and increased the ability of single MuSCs to form colonies and to differentiate into myotubes including their resumed regeneration potential *in vivo*. This treatment also led to the restoration of forced production by muscles that were transplanted with untreated aged MuSC. Similar results were obtained by using transplanted, transiently reprogrammed, aged human MuSCs that resulted in increased longitudinal bioluminescence imaging signals compared with untreated MuSCs from the same individual, and comparable with those observed using young MuSCs. There were not any evidence of neoplastic lesions or teratomas during the necropsy of the animals (478). These studies successfully showed that age related pathologies are reversible by partial reprogramming and that such a strategy leads to the reversal of aging clock. Given that the identities of the treated cells did not change with such treatments, it is evident that reprogramming can be distinctly uncoupled from the de-differentiation events and emergence of stem cell traits which have, thus far, been a major hurdle for

the use of reprogramming of cells and tissues in aging organisms.

4. CONCLUSIONS

Within the last two centuries, we have witnessed a great deal of progress in understanding the cell-centric causes of aging. Based on these diverse theories of aging, just in the past few decades, many therapeutic options have emerged that all have contributed to extend the health-span and life-span of model organisms to human beings. We have been able in regulating the aging process by manipulating the telomeres, and the signaling pathways, and have developed technologies to remove or restore the senescent cells within aging tissues. We have been able to force the differentiated cells to gain pluripotency and have used partial reprogramming in restoring the epigenome, to an earlier, more youthful state. Metformin and NAD^+ are at the forefront of aging therapeutics and the idea that a mixture of DHEA, GH and metformin can reset the aging clock, has opened new possibilities to even reverse the aging processes. We are certain that the trajectory of our understanding of aging will significantly increase in the next decade and new modes of treatment for aging, undoubtedly, will be unveiled.

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Abbreviations: Dietary restriction (DR), Calorie restriction (CR), AMP-activated protein kinase (AMPK), *Caenorhabditis elegans* (*C. elegans*), Essential amino acids (EAA), Cerbrovascular accident (CVD), 8-oxo-2-deoxyguanosine (oxo^8dG), Nuclear DNA (nDNA), Mitochondrial DNA (mtDNA), Oxidative phosphorylation (OXPHOS), Nicotinamide adenine dinucleotide (NAD), tryptophan (Trp), Nicotinamide (NAM), Nicotinamide mononucleotide (NMN), Nicotinamide riboside (NR), 5′-phosphoribosyl-1-pyrophosphate (PRPP), NR kinases (NRKs), NMN adenylyl transferases (NMNATs), NMN adenylyltransferases (NMNAT1-3), Nicotinamide phosphoribosyltransferase (Nampt), β-amyloid (Aβ), S-adenosyl methionine (SAM), Carnosine (beta-alanyl-L-histidine), IκB kinase complex (IKK), N-*tert*-butyl-*α*-phenylnitrone (PBN), Hydrogen sulfide (H_2S), Transsulfuration pathway (TSP), Manganese superoxide dismutase (SOD), Age-Related Diseases (ARDs), Histone deacetylase (HDAC), Dipeptidyl peptidase 4 (DPP4), Human umbilical cord endothelial cells (HUVEC), Janus kinase (JAK), Interluekin (IL), Tumor necrsis factor (TNF), Dehydroepiandrosterone (DHEA), 4-hydroxytamoxifen (4-OHT), Insulin growth factor (IGF), Muscle-derived stem/progenitor cells (MDSPCs), Nuclear factor erythroid 2-related factor (NRF2), Somatic cell nuclear transfer (SCNT), Human embryonic stem cells (hES), Muscle stem cells (MuSCs), OCT4, SOX2, KLF4, c-MYC, (OSKM), OCT4, SOX2, KLF4, c-MYC, LIN28, NANOG (OSKMLN), Embryonic stem cells (ESC), Induced pluripotent cells (iPS), Growth and differentiation factor (GDF), Senescence-associated mitochondrial dysfunction (SAMD), Senescence-Associated Secretory Phenotype (SASP), Reactive oxygen species (ROS), Hutchinson-Gilford progeria syndrome (HGPS), Werner Syndrome (WS), Duchenne Muscular Dystrophy (DMD) , Unfolded protein response (UPR^{mt}), poly-ADP-ribosylation (PARylation), Poly(ADP-ribose) polymerase protein (PARP), Clustered regularly interspaced short palindromic repeats (CRISPR)

Key Words: Aging, Senescence, Immuno-senescence, Treatment, Senotherapeutics, Senolytics, Senomorphics, Anti-Inflammaging, Aging Reversal, Review

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