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Cell-centric hypotheses of aging

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1. ABSTRACT

Aging in mammals results in numerous age related pathologies such as diabetes, and Alzheimer's disease which ultimately lead to organ failure and the demise of the organism. Numerous cell-centric hypotheses have attributed the disorders of aging to lie downstream to age dependent cellular damage to biologic signaling pathways, bio-informational molecules, telomeres, organelles, and stem cells. Here, we review these cell-centric causes of aging that range from the disposable soma theory, to somatic mutation theory, and free radical theory, to theories that ascribe aging to DNA damage and methylation (DNAaging and DNA superaging), impairment of autophagy (GarbAging), telomeric attrition, senescence, immunoscencence and inflammaging. Others view that aging is caused by MitoAging, NutrimiRaging and miRagings to exhaustion of stem cell pool. Together, the current models of aging, show the existence of damage to different cellular compartments. However, it is not yet clear which, if any, of these cellular damages represent the most proximal cause of aging.

2. INTRODUCTION

At the organismal level, aging is evident in all human beings by loss of the ability to reproduce, and damage and loss of function in organs, tissues, and cells. Many theories of aging have been offered, yet, none of these theories can explain all the cellular

and organismal changes which occur with aging. Importantly, the most proximal cause of aging is currently unknown and it is not yet evident as why the epigenetic clock that accounts for the methylation status of a host of genes so precisely, can predict aging and how these methylations are induced and drive the aging process. Here, we discuss the current theories of aging.

3. CELL-CENTRIC HYPOTHESES OF AGING

3.1. Disposable soma theory

Perhaps one of the earliest theories of aging is the so-called disposable soma theory. According to this theory life maintains a balance in investing its energy resources between maintaining itself by repair processes and those which are required for procreation and that aging occurs when the body invests more of its energy for somatic repair or forgoes of such an investment leading to cell death (1-2).

3.2. Somatic mutation theory

The somatic mutation theory proposes that accumulation of DNA mutations can lead to tumorigenesis and senescence (3). Consistent with this theory, studies in prokaryotes, yeast, and mammalian cells have demonstrated that oxidants are mutagens and although, there is no argument that indeed point mutations in oncogenes or tumor suppressor genes can cause cancer, there is as yet no definitive proof that such mutations in the DNA can drive all the hallmarks of aging. Yet, the anti-oxidant mechanisms are sufficiently robust and can revert back to normal, the oxidized lipids, proteins and nucleic acids (4-8).

3.3. Free radical theory and rate of living hypothesis

According to the free radical theory proposed by Denham Harman, oxidative stress is one of the most important drivers of aging. He drew parallels between the effects of aging and those that are inducible by ionizing radiation, mutagenesis, cancer, and cellular damage (9). This theory gained further traction with the identification of the enzyme, superoxide dismutase (SOD), which provided the first compelling evidence, that superoxide anions (O^{-2}.), can be generated *in vivo*, and got further boost from the subsequent identification of a host of anti-oxidant defense mechanisms (7,10). This concurred with the idea, that species with a high metabolic rate, age faster and have a shorter life-span (11-12). This theory was also consistent with the “rate of living” hypothesis that senescence results from energy consumption (11,13). These two hypotheses merged when it was shown that mitochondria are the principal source of endogenous oxidants and generate O^{-2}. and that faster respiration leads to the generation of more oxygen radicals, which drive significant damage to cell and its constituents (14-20).

In mammalian cells, reactive oxygen species (ROS) are comprised of O^{-2}., H_2O_2, and .OH. ROS are generated by 5-lipoxygenase and NADPH oxidase in the mitochondria and by the mitochondrial electron transport chain (ETC) by donation of electrons by NADH or succinate to complexes I and II. Peroxisomal fatty acid metabolism generates H_2O_2 , and reactions by cytochrome P-450 that metabolize xenobiotic compounds, mostly of plant origin, by catalyzing their univalent oxidation or reduction can also generate oxidants. Phagocytic cells release ROS as a mixture of oxidants and free radicals, including O^{-2}., H_2O_2, NO. and release hypochlorite as a “respiratory burst” in response to and in attempt of killing pathogens (3). Other sources of oxidants are enzymes that, often, in a tissue-specific manner, generate ROS under normal or pathological conditions (21).

Under normal conditions, the on·slaught damage by ROS is prevented by a host of anti-oxidant defense mechanisms that include enzymatic scavengers such as sodium dismutase (SOD), which cause the dismutation of O^{-2}. to H_2O_2, as well as catalase and glutathione peroxidase (GPX), which convert H_2O_2 to water. Also included in these defense mechanisms are GSH reductase, and dehydroascorbate reductase which are involved in the reduction of oxidized forms of small molecular anti-oxidants as well as thioredoxin reductase which maintains protein thiols. Ascorbate (vitamin C), urate,

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and glutathione (GSH) act as hydrophilic radical scavengers whereas tocopherols, the major forms of vitamin E, phenolic compounds, flavonoids, carotenoids, and ubiquinol act as lipophilic radical scavengers. Glucose-6-phosphate dehydrogenase regenerates NADPH and maintains a reducing environment (3). Although diverse lines of evidence exist that support Harman's theory, this idea can not explain all the age related pathologies, and although ROS is widely accepted to contribute to aging, substantial gaps in our knowledge still persist (22).

3.4. DamAging

According to the damage theory of aging, aging is due to the occurrence of widespread genetic changes and instability of the major informational bio-molecules, including DNA, RNA, proteins, carbohydrates and lipids (23). Such damages are considered to be major causal factors that drive the age-related alterations and diseases, and lead to decreased health-span and life-span (24-27). Random alterations in the synthesis and change in the structure of bio-molecules are thought to be the underpinning of some, but not all, of the physiological changes that we witness in aged tissues. However, the full extent of the frequency, and characteristics of changes that occur in the cellular and molecular machinery and their driving forces have not been fully realized.

Particularly vulnerable to damage are long lived molecules that exist within cells or persist for a long time in the extracellular matrix. However, it is not clear as whether such damages are causal or casual and more work is clearly needed to define the importance of such damages and whether they are unique to all cells or a subset of cells and tissues. Also, there is a need to know whether such changes cause damage or are ways that cells protect themselves from further damage. The cause of these damages have long been considered to be ROS, however, the possibility that not all damages might be related to ROS and that some damages might be due to other causes such as UV, impact of different wavelengths and environmental toxic agents can not be ruled out. Indeed, these damages might be due to the inherent and progressive failure of the damage response pathways. Based on existing models, it is clear that failure of damage repair can lead to the shortening of life-span and progeria. For example, mice with defects in DNA repair genes show premature aging that are indistinguishable from those that are displayed by wild-type aged mice (27). Similarly, a defective ubiquitin ligase/co-chaperone (Carboxyl terminus of HSP70-interacting protein) reduces life-span and causes accelerated age-related pathologies in mice (28).

3.5. DNAging and super DNAging

There are other causes for damage to biomolecules, by endogenous factors such as replication errors, oxygen free radicals, glucose and oxidative sugars and body heat and exogenous factors such as ionizing radiations and DNA damaging agents, UV rays, xenobiotics, viruses, chemicals and dietary carcinogens. Although cells have developed defense mechanisms to protect the biomolecules from these damages and have mechanisms to repair them, aging leads to the erosion of the robustness of such systems, and hence, with age, the rapidity by which such changes occur and the number of damaged molecules, increases progressively.

The DNA damage theory arose from the idea that aging might result from DNA damages that remain un-repaired and that such damages contribute to the age related pathologies. Consistent with such a theory, defects in the DNA nucleotide excision repair are associated with accelerated aging in mice while certain single nucleotide polymorphism in DNA repair genes are associated with extended life-span in humans (28-32). DNA endures damage such as single- and double-strand breaks, adducts, and crosslinks and mutations throughout life by a host of internal and environmental factors (33). Single strands of DNA are repaired via base excision repair (BER) and nucleotide excision repair (NER) and its subpathways. Double strand DNA breaks (DSB) are repaired by the non-homologous end-joining (NHEJ) and homologous recombination (HR) pathways. DNA damage is identified by the accumulation of 8-hydroxydeoxyguanosine (oxo^8dG) residues and polycyclic aromatic hydrocarbon adducts, while mutations, which may be caused by imperfect DNA replication, are specific changes that occur in specific nucleotide sequence.

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It has been estimated that DNA damage occurs in mice at a rate of 25 to 115 times per minute in each cell, or about 36,000 to 160,000 per cell per day (34). Although, DNA replicates with a fairly high fidelity, the DNA polymerase in humans is subject to making errors at a rate of 1 per every 100,000 nucleotides which are then mostly corrected by various DNA enzyme repair processes (35). After the cell division is finalized, any incorrectly paired nucleotides remain as permanent mutations. Once the genes of DNA repair enzymes, themselves, are damaged, the mutation rate increases at a faster rate. Some of such enduring mutations are carcinogenic while other types of damage might change the gene expression, increase the rate of senescence or apoptosis and shorten the life-span (36-39).

Damage to the ataxia-telangiectasia mutated (ATM) kinase which detects DSBs is associated with genomic instability, DNA repair defects, immune deficiency, and premature cellular senescence that can be rescued by p53 deficiency. This disease also generates elevated ROS levels that cause further damage to the DNA. At the organismal level, the disease causes cerebellar degeneration, progeroid aging and cancer (40-41). Lending credibility that DNA mutations can be pathogenic and may shorten life-span, are a spectrum of human diseases such as Hutchinson-Gilford progeria syndrome (HGPS) that all cause premature aging. HGPS syndrome is caused by a mutation at the *LMNA* locus that encodes proteins of the nuclear laminae. Mutations in *LMNA* have also been reported in several other atypical progeroid syndromes (42). Werner syndrome (WS) that also causes progeria is due to mutations in the *WRN* genes (43-44). There are reports of other progeroid disorders including neonatal progeroid syndrome (NPS) or Wiedemann-Rautenstrauch syndrome that present with an “old-man” appearance since birth or childhood. These are thought to be potentially caused by DNA repair defects (45-46). Although, DNA mutations might be pathogenic, their overall contribution to age related shortening of life-span is debatable. For example, increased genomic instability has not been found to be necessary for shortened life-span in DNA repair deficient mice. Defects in the *Pms2* gene, that normally corrects DNA base pair errors, increases the frequency of DNA mutations in all tissues by about 100-fold, yet, it does not shorten life-span in mice (47-48).

As compared to “averagely” aged humans, in nonagenarians (90–99 years), centenarians (100–109 years) and super-centenarians (110 years and older), the prevalence of diseases, such as cancer, cardiovascular disease, diabetes and dementia, is lower (49). This suggests that such long lived individuals possess better defense and housekeeping mechanisms and superior genetics, and chromosomal, telomeric and DNA stability that curtails the extent of such damages. Additional environmental factors such as diet, physical activity, and stress free life-style might be at work in keeping the damage to molecules at bay in these long lived humans (49).

3.6. DNAMethylAging

One of the cardinal features of aging, is the progressive and relentless life-time methylation of the DNA. The epigenetic theory of aging emerged from the observation that baseline DNA methylation levels progressively drift by aging, a process, named as “epigenetic drift”. These changes can be observed in the identical genetic backgrounds such as monozygotic twins (50). There are other *locus*-specific DNA methylation changes that are not dependent on gender or tissue type and reproducibly occur in all aged people. In fact, the process is so precise that the true biological aging can be deciphered from the methylation state of a handful of CpG sites (51). The DNA methylation, is deeply embedded in nature as an evolutionarily conserved process in diverse species, not only for epigenetic modification for gene silencing but also for regulation of longevity and aging (52-54). In some aging tissues, one can observe, a stochastic age-associated increase in gene expression, that is referred to as transcriptional noise (55).

Aging appears to be plastic and not fixed, to be inducible and yet reversible and longevity is known to be epigenetically controlled by specific alterations in the chromatin state. It is remarkable that epigenetic changes, not only are responsive to aging, they can act as potent drivers of the aging processes.

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In fact, DNA methylation patterns that are associated with gene repression are known to be dynamically changing with age and epigenome appears to act as a sensor that gauges age dependent changes due to DNA damage, environmental stresses, or inflammation and sets the cellular response to the development of metaplasia to senescence (56-58). The idea, that the DNA methylation and aging are intertwined, dates as far back as the 1987, when it was realized that aged tissues and senescent fibroblasts exhibit low levels of 5mC (59-60). This initial idea has been expanded remarkably by genome-wide analysis of methylome that clearly shows, that DNA methylation patterns, are age dependent in aging tissues and across many species (50, 61). The erosion of DNA methylation patterns involves both locus-specific hypermethylation and hypomethylation (50, 62-64). Global hypomethylation appears to signify the loss of integrity of constitutive heterochromatin, that is seen in various eukaryotes, ranging from yeasts to humans (65). The first genome-wide analysis on aging revealed, that there is an equal extent of 5hmC gain or loss, in human mesenchymal stem cells (hMSCs). These loci had distinct distribution patterns with hypo-hydroxymethylated sites being highly represented at CG-poor regions whereas the hyper-hydroxymethylated sites occurred mainly at CGIs and gene bodies (66).

Some epigenetic changes such as hypomethylation foci or methylation changes that develop at specific CGIs and may lead to transcriptional deregulation during aging are also represented in replicatively senescent cells (67-71). There are some specific epigenetic signatures that are independent from the age of the individual that correlate well with the number of replications in both fibroblasts and hMSCs (72-75). Some of these changes may play a causal role since it is known that treatment of cells with inhibitors of DNA methylation causes senescence (76). Both replicative and oncogene inducible forms of senescence have been shown to lead to an increase in the biological age as gauged by the epigenetic clock (77). However, such changes are not universal, since DNA damage induced senescent cells, do not endure such changes (77).

Foci of hypermethylation mainly occur at gene specific CG islands during aging which sometimes alter gene expression (78). Some of these hypermethylated genes also appear in age induced diseases, impaired immunocompetence in the elderly and in cancer cells (79-88). The age inducible hypomethylations occur in heterochromatic regions of the DNA. In human DNA, this includes repetitive elements and transposons which contain the majority of methylated CG dinucleotides as well as CG-poor regions which reside close to certain genes (61, 89-91). The so-called “open sea regions” include megabase regions that also have a low CG content (92).

Moreover, the methylation of histone which is controlled during the development, and is required for the maintenance of stem cell plasticity, is also intimately linked to aging (93-98). Histone methylation is an active process that requires the trithorax group of proteins, which trimethylate histone H3 at lysine 4 (H3K4me3), a histone mark that is required for gene activation. Indeed, whereas in-activation of a H3K4 demethylase shortens life-span, in-activation of trithorax and several H3K4 methylases has been shown to extend life-span in *C. elegans* (99).

The epigenomic changes start early in life as early as fertilization, continue during the development and in the pre-implantation embryos, when massive de-methylation, renders germ cells totipotent (50, 100). Even during prenatal development, the methylome is exquisitely responsive to the maternal diet (101). The Dutch Hunger Winter study showed, that embryos from mothers who experience famine, develop hypomethylation and hypermethylation of several DNA loci, and later in life, develop many health issues such as cardiovascular disease, hypertension, impaired glucose homeostasis to obesity (102-103). Even depression of the mother can alter the methylation status of the imprinted genes which, later in life, exposes the individual to diseases (104). Throughout the life of an adult, the methylation status of DNA. is also known to drift with age based on such lifestyle choices as diet and calorie intake, physical activity as well as a host of chemical, physical, biological, psychological and behavioral factors (105-

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106). For example, physical activity has been shown to reduce the risk of developing cancer and mortality (107-110).

Unfortunately, the epigenome which molds genomic information. loses its luster with age due to the multitude of nutritional and intracellular and extracellular, environmentally driven, stresses that deteriorate the genomic integrity. Although, this loss of genomic integrity persists, there is hope that rejuvenating interventions can be instituted that reverse the age-dependent epigenetic and gene expression drifts, as well as to normalize the biochemical changes, including protein aggregation, oxidation of informational macromolecules, and glycation (111). For example, some epigenetic changes that occur both in aging and by senescence have been shown to be reversible by reprogramming of cells into induced pluripotent stem cells (iPSCs) (112-115).

3.7. GarbAging and impairment of autophagy

Autophagy is a housekeeping and protein quality control mechanism that is required for the maintenance of cellular health by removing damaged or defective proteins and organelles by the process of macroautophagy and mitophagy. Autophagy gets activated by stress including caloric restriction, and endows cells stress resistance and longevity (116-120). It has been shown that in *C. elegans,* increased autophagy and expression of autophagy genes, such as *bec-1*, *Atg-7* and *Atg-12*, are required for the extension of life-span (121-124). Unfortunately, the action of removal of damaged parts degrades with aging, leading to the accumulation of waste products by impaired autophagy, accumulation of defective mitochondria due to decreased mitophagy (GarbAging), with the final outcome of development of cellular senescence and age-related degenerative diseases (125-133). In mammalian liver, autophagy declines during aging, by a progressive decrease in the expression of lysosomal-associated membrane protein 2 (LAMP2) which acts as a receptor for chaperone-mediated autophagy (134). Prevention of this age induced decline in LAMP2 suppresses the accumulation of damaged proteins and improves hepatic function (135).

AMPK signaling a positive regulator for autophagy, controls autophagy through mTOR and ULK1 signaling, and leads to reduction in metabolism (136-137). AMPK regulates the formation of autophagosomes whereas mTOR inhibits autophagy (137-138). mTORC1 interacts with ULK1 complexes and regulates the metabolic balance between protein and ribosome synthesis, and the catabolic processes that require autophagy. Mammalian ULK1, an orthologue of yeast Atg1, acts as a gatekeeper for autophagosome formation by binding to phagophoric membranes and enhancement of the function of autophagic conjugation systems (139). PI3K-AKT which activates the mTOR-mediated biosynthetic processes, represses autophagic degradation. Active mTORC1 becomes associated with the ULK1/ATG13/FIP200 complex, phosphorylates ULK1 and represses its protein kinase activity. On the other hand, AMPK can induce autophagy by directly binding to the ULK1 complex and phosphorylating ULK1 and by inhibiting the activity of mTOR complex (mTORC1) by dissociating mTORC1 from the ULK1 complex, phosphorylating the Raptor, a regulatory component of mTORC1, or by phosphorylation of tuberous sclerosis protein 2 (TSC2) (137, 140-143). AMPK enhances autophagosome formation by the activation of SIRT1 signaling. SIRT1 participates in autophagy by complexing and deacetylating several autophagy proteins including Atg5, Atg7, and Atg8, that in the absence of SIRT1, are acetylated leading to the accumulation of damaged organelles in $SIRT1^{-/-}$ mice (144). The activation of FoxO1 and FoxO3a transcription factors also increases the expression of several autophagy-related genes leading to enhanced autophagocytosis (145-146).

3.8. MitoAging

Following the free radical theory, in the early 1980s, Jaime Miquel proposed oxyradical-mitochondrial DNA damage hypothesis. According to this hypothesis since the synthesis of the mitochondrial DNA (mtDNA) takes place at the inner mitochondrial membrane, at the vicinity of the sites that highly reactive oxygen species are formed, the mtDNA is subject to oxidative damage. In irreversibly

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differentiated cells, the damage entails mutation, and in-activation or loss of the mitochondrial genome leading to changes in the structural mtDNA genes for the 13 hydrophobic proteins of the respiratory chain and ATP synthase and the mitochondrial rRNAs and tRNAs. This, in turn, prevents the macromolecular turnover and organelle fission and ceases the 'rejuvenation' of the mitochondria (147). Thus, the fixed post-mitotic cells, deprived from the ability to regenerate their mitochondria, sustain a decrease in the number of functional organelles, develop dwindling ATP production, and curtail ATP-dependent protein synthesis and specialized physiological functions. Such an extensive decline in the cell energy reservoirs, therefore, confers to cells an aging phenotype that ultimately leads to age related degenerative diseases. In fact, mitochondrial integrity deteriorates as a function of age and defects in the mitochondrial function have been implicated in over 100 diseases. Mitochondrial DNA mutations and impaired oxidation have been shown in aging and age-related degenerative diseases such as atherosclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease, amyotrophic lateral sclerosis (ALS), cardiomyopathies, and more importantly diabetes mellitus that further drives multi-organ and systemic damages (148).

Mitochondrial dysfunction can be caused by a host of causes namely, defects in ETC enzymes (Complexes I - IV), loss of of the electron carrier, coenzyme Q10, insufficient energy fuel supply or oxygen due to ischemia or anemia, or excessive membrane leakage, that results in insufficient mitochondrial inner membrane potential for ATP synthesis by the F0F1-ATPase. Although such defects, to some extent, can be overcome by mitochondrial biogenesis, at certain critical ATP level, cell death ensues. Defective OXPHOS may be caused by abnormal the mitochondrial function resulting from inherited or acquired mutations in the nuclear (nDNA) or mitochondrial (mDNA) (149).

Aging has also been shown to lead to the accumulation of point mutations and large-scale deletions of mtDNA, decrease in mitochondrial respiratory function, increase in mitochondrial production of ROS, which in turn, leads to oxidative damage to DNA, proteins, and lipids and enhanced apoptosis. Tissues that are highly dependent on oxygen and mitochondrial OXPHOS including cardiac, skeletal and smooth muscles, central and peripheral nervous system, kidney, and the insulin-producing pancreatic beta-cells are particularly susceptible to the mitochondrial dysfunction (149-150).

The decline in the mitochondrial function might emanate from mutations in mtDNA. Somatic mutations in mtDNA, senescence and associated age related decline in the mitochondrial function and aging at the organismal level appear to result from several causes namely, the oxidative environment within mitochondria, absence of protective histones in mtDNA, and the lack of efficient repair mechanisms for mtDNA (151-152). Consistent with this, mutations in mtDNA is associated with aging phenotypes in humans. Moreover, a mutation in the proofreading exonuclease domain of the mtDNA polymerase γ, which is associated with mtDNA mutations, leads to a decline in the mitochondrial function, premature aging and a reduced life-span in mice (153-158).

In post-mitotic tissues the levels of oxo^{8}dG are significantly higher in mDNA than nDNA, likely due to the absence of protection shields such as histones and lack of systems that maintain the integrity of DNA replication (159). Although mitochondrial DNA can bear mutations, there is as yet no available evidence that such DNA mutations are the direct cause of cellular aging nor there is any evidence that repair of such mutations can prolong the life-span (160). Moreover, mitochondrial mutator mice that exhibit 500-fold higher mutation burden than normal mice, fail to show rapidly accelerated aging indicating that mtDNA mutations do not shorten the life-span (161). Additionally, despite age dependent accumulation of a higher level of oxo^{8}dG in nDNA and mtDNA, mice which are heterozygous for a mutation in the mitochondrial enzyme that processes superoxide, Sod2, and exhibit life-long reduction in MnSOD activity, fail to show an accelerated aging (162).

The mammalian nuclear factor-erythroid 2-p45 derived factor 2 (Nrf2) and skinhead family member 1 (SKN-1) in *C. elegans* represent potent defense against oxidative stress and are known to

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increase life-span in model organisms (163-168). These pathways erode and become less active or get dysregulated in aging and in age-related degenerative diseases (163, 169-170). Nrf2/EpRE signaling regulates the basal and inducible expression of many antioxidant enzymes and the proteasome. The antioxidant defense enzymes responsive to Nrf2, include NAD(P)H:quinone oxidoreductase-1 (NQO1), heme oxygenase 1 (HO-1), glutathione S-transferase (GST), glutamate cysteine ligase catalytic subunit (GCLC) and the cystine/glutamate (xCT) transporter which is involved in the adaptive up-regulation of GSH synthesis (171-175). Although, under normal conditions, Nrf2 is targeted for proteasomal degradation, by its binding to the Kelch-like ECH-associated protein (Keap1), activators of the Nrf2 pathway unleash stress-induced proteasomal activity that leads to the removal of oxidized proteins. Disruption of the basal ubiquitin-dependent degradation of Nrf2 by the 26S proteasome, leads to its nuclear accumulation and gene induction and restores redox homeostasis by increasing antioxidant/electrophilic response element-mediated (ARE/EpRE) expression of phase II and antioxidant enzymes (176). The overall activity of Nrf2 is regulated by modulation of its transcription by PI3K, P62, CBP, and BRCA1, post-translational mechanisms, and its interactions by other proteins (177). Nrf2 is negatively regulated by, Keap1, Bach1, c-Myc and a host of microRNAs. Nrf2 has been identified by siRNA screen to be the driving mechanism for the Hutchinson-Gilford progeria syndrome (HGPS), that is caused by constitutive production of progerin, a mutant form of the nuclear architectural protein, lamin A, that leads to the nuclear sequestration of Nrf2 and impairs its transcriptional activity and consequently increases chronic oxidative stress, premature aging, and ultimately, invariably, causes death (178). An additional determinant of progeria in HGPS appears to be related to the impaired transcriptional activity of Nrf2, and the abnormal nuclear lamina-mediated mislocalization in MSCs (178). There are additional evidence that directly places Nrf2 as being involved in age related pathologies such as age induced fibrosis and for this reason, Nrf2 is a promising target for the development of novel pharmacologic or genetic therapeutic regimes (179). Nrf2 was recently found to be responsive to the apocarotenoid, bixin, an FDA-approved food additive derived from the seeds of the achiote tree (*Bixa orellana*). Bixin suppressed acute UV-induced photodamage and reduced epidermal hyperproliferation and oxidative DNA damage in $Nrf2^{+/+}$ but not $Nrf2^{-/-}$ mice (180).

Preserving the mitochondrial function by a cellular stress response pathway which involves activating the mitochondrial unfolded protein response (UPR^{mt}), leads to increased life-span in *C. elegans* (181). Proper the mitochondrial function appears also to be significant to the maintenance of tissue homeostasis. For example, cell proliferation appears to be intimately linked to the mitochondrial 1C metabolism-induced redox homeostasis (182). Fortunately, age-associated damage to the mitochondrial respiration can be counteracted by exercise and it is becoming clear that the maintenance of the mitochondrial function can be used to delay age related decline and as a successful avenue to extend human life-span (183).

3.9. Telomeric attrition

Telomeres are molecular clocks that count the number of cell divisions and are comprised of repetitive TTAGGG sequences at the ends of the chromosomes. In mammalian cells, telomeric ends have a a protective “t loop” a higher-order structure, comprised of a terminal 3′ single-stranded tail, the so-called “G” strand overhang, which is buried into adjacent double-stranded repetitive telomeric DNA. This loop, in turn, is stabilized by a displacement of “D” loop that is formed between the invading end of the telomere into adjacent double-stranded DNA (184). The deterioration of G strand overhangs is protected by a specialized complex that maintains their integrity, and prevents their shortening and fusion with neighboring chromosomes during replication. This complex is made of reverse transcriptase, telomerase (*TERT*, or *hTERT* in humans) and its catalytic RNA sub-unit, *TERC* that extends telomeres during S phase, therefore, preventing the natural shortening of telomeres (185). While telomerase is expressed in embryonic and adult male germline cells, it is absent in normal somatic cells such as fibroblasts. These cells have very low levels of telomerase activity, and following each round of cell division, telomeres shorten in each

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successive generations. Senescence ensues when cells ultimately end up having critically short telomeres through a process that may involve loss of the t loop structure and/or “uncapping” due to the loss of protective proteins. Such uncapped telomeres are then recognized by the cell cycle checkpoint machinery as DNA damage, which causes cell cycle arrest (186). Lack of repair of the telomeric ends leads to the erosion and shortening of telomeres following each cell division. In cells with an intact cell cycle checkpoints (G1 cell cycle block), shortening of telomeres, leads to senescence. In cells that have in-activated cell cycle checkpoints and exhibit chromosome breakage and mitotic catastrophe, and shortened telomeres and telomeric end-to-end fusions, lead to the cellular crisis (185).

The use of telomerase deficient mice has served as a model system for examining the adverse organismal and cellular consequences of lack of the telomeric maintenance. Besides mechanisms which maintain the integrity of DNA and prevent its damage, it appears that the capping function of telomeres is required to prevent the tell-tale signs of aging including activation of p53, and for prevention of stem cell depletion and decline in stem cells that cause tissue atrophy and compromised mitochondrial function, and loss of maintenance of bioenergetic homeostasis in tissues (187).

Dysfunction of the telomeric maintenance leads to various diseases such as dyskeratosis congenita that results from mutations in the gene encoding dyskerin (DKC). DKC is proposed to be a ribosomal RNA similar to the yeast protein which is involved in production of rRNA and it interacts with telomerase and stabilizes the RNA in this complex (188). On the other hand, mutation in *TERT* has been shown to lead to dysfunction of highly proliferative bone marrow cells resulting in aplastic anemia (189). Late-generations of *TERC*-deficient mice show some signs of accelerated aging (190-191).

3.10. Senescence

Hayflick and Moorhead (192) discovered that, after a limited number (50-80) of cell divisions, fibroblasts experience a permanent loss of cell proliferation and enter a state of replicative senescence. Besides replicative senescence which occurs in aging tissues, for example as a result of telomere shortening, mitogenic signals, oxidative stress or other types of damage, there are other forms of senescence. This includes DNA damage induced senescence and oncogene induced senescence which remain largely indistinguishable from replicative senescence (193-196). Senescence is intimately linked to the remodeling during embryonic development, in normal placental function as well as wound healing, and stress response (197). In healthy tissues, damaged cells undergo apoptosis and are replaced by freshly divided cells and, this division, not only removes the damaged cells, cell division, dilutes persisting damage in daughter cells. In case, that the damage is more severe, senescence is engaged to stop the cell replication, and, to prevent premalignant cells with one or two oncogenic mutations, to undergo further tumorigenic changes.

Senescent cells exhibit phenotypic and morphological changes and expansion of their cytoplasm. They also have shortened telomeres, and show an increased expression of senescence markers including senescence-associated β-galactosidase (SA-β-Gal) and of cyclin-dependent kinase inhibitors including p16 and p21 (198-200). *CDKN2A* locus is under epigenetic control by the gene-silencing complex, polycomb group proteins. Polycomb-repressive complex 2 (PRC2) along with its catalytic sub-unit, EZH2 trimethylates lysine 27 of histone H3 (H3K27me3). This, in young cells, in turn, recruits PRC1 which further modifies chromatin to a state that silences genes including cyclin-dependent kinase inhibitor, p16 (201). However, upon aging, the levels of EZH2 mRNA and protein levels, and the level of H3K27me3 at the *CDKN2A* locus dwindles, and this leads to a progressive increase in p16 expression, that causes an irreversible cell-cycle arrest and cellular senescence (202-203). JMJD3, which is inducible by replicative exhaustion, the transcription factor NFκB, or oncogenic stress can compete with EZH2 in occupying the *CDKN2A,* and by virtue of demethylating H3K27me3 can allow p16 expression and senescence (204-206).

p16 and p21, are well established senescence-associated markers that their expression is increased, during replicative

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senescence and DNA damage induced senescence (207). The activation of the p53 and Rb proteins is thought to be required for induction of senescence to prevent and suppress tumor development and, for this reason, senescence is regarded as a tumor suppressor response mechanism (208-210). Despite being a predominant tumor suppressor, once tumors occur, senescent cells provide a pro-oncogenic milieu and promote the growth of epithelial tumors (211).

Senescent cells exhibit a specific senescence secretome, the so-called Senescence-Associated Secretory Phenotype (SASP). The true microenvironmental impact of SASP and its composition varies based on the tissue and cell types which reinforces cell cycle arrest. SASP amplifies the innate immune responses, particularly those that involve the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway (cGAS-STING pathway) in response to the accumulation of cytoplasmic DNA (cytoplasmic chromatin fragments, mtDNA and cDNA)(212). SASP also leads to the immune mediated clearance of cells that have the potential to cause cancer (213). Attaining SASP, is driven by and requires, a host of cellular activity including metabolic regulators and cell survival-related transcription factors, miRNAs, RNA stability, autophagy, chromatin components, and metabolic regulators as well as DNA damage response (DDR), stress kinases, alarmin, inflammasome and inflammation. Temporally, SASP matures through an early DDR associated phase, early self amplification phase and a late phase. It is this latter phase that produces the hallmarks of SASP, namely, the anti-proliferative state, clearance of senescent cells, as well as chromatin remodeling. This stage also impacts the control of mRNA translation and intracellular trafic, and is responsible for the activation of transcription factors such as NFKB, c/EBP, release of inflammatory cytokines such as IL-6 and TNF-α and of chemokines, extracellular proteases, growth factors and bioactive lipids (214-215). p38MAPK has been described as an independent regulator of SASP phenotype (216).

Many mouse models and human diseases that cause early senescence also lead to premature aging (217). Senescent cells contribute to aging through separate mechanisms. Cellular senescence renders cells replicatively in-active and senescent cells through release of inflammatory cytokines and secretion of proteases and other factors to their environment can disrupt tissue function. Senescent cells seem to induce senescence in neighboring cells and contribute to the age related pathologies. For example, transplanting a relatively small number of senescent cells into young mice led to the spread of cellular senescence in host tissues and caused persistent physical dysfunction while introduction of fewer senescent cells to old animals reduced their life-span (218). Senescence in progenitor or stem cells is actively suppressed for example, *Polycomb* group repressor, Bmi1, negatively controls senescence in hematopoietic stem cells (211, 219). However, these cells are not immune to this process and their senescence occurs with normal aging, DNA damage, environmental stress, and telomeric dysfunction. Cease in stem cell replication, due to senescence, halts the normal tissue renewal and leads to tissue atrophy which is typical of aging tissues.

3.11. Immunosenescence, inflammaging and senoinflammation

Aging leads to a progressive decline in the immune responses leading to a state of dysregulated immune function (immunosenescence), and development of a low grade and sterile inflammation (inflammaging) in aging tissues as a result of an imbalance between pro- and anti-inflammatory responses to environmental pathogens including gut microbiome or endogenous, self, misplaced, or altered molecules. The prevailing view is that during aging, the immune cells fail to mount an efficient innate and adaptive immune program in response to antigens or environmental stimuli (e.g. ROS). As a consequence, the inflammatory response does not subside and becomes chronic in aging tissues (inflammaging) and provokes molecular inflammatory signals in such tissues (220-222). Inflammaging is the expansion of the network and the remodeling theory of aging (223-225).

Immunosenescence is primarily characterized by involution of the thymus, reduced reactivity of immune cells and response to

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vaccination or a new antigen load, auto-reactivity, autoimmunity and a lower anti-cancer and anti-microbial responses and phagocytosis (226). Immunosenescence also reduces cellular superoxide production, and naïve:memory cell ratio and leads to the expansion of mature cell clones (227). Together, the failure of autoreactive and autoimmune processes, loss of ability to remove damaged molecules and organelles and emergence of senescence, progressively fuels a chronic state of inflammation locally and systemically. These events result in a greater susceptibility of aging population to cardiovascular disease, Alzheimer's disease, and a greater rate of mortality (228-230). Thus, inflammaging and immunosenescence are considered as major targets for devising strategies to reverse age related pathologies and disorders.

The adaptive arm of immunity is more severely impacted by age than the innate immunity, (231). However, only a limited number of phenotypic and functional changes have been observed in the T cell arm of the adaptive immunity (232). Moreover, cross-sectional studies of young and old population show a vastly varied distribution of immune cell types in the blood, and to some extent, a diverse aberrancy in the functional integrity of these cells (231).

Some studies have revealed biomarkers of immune aging 'immune signatures' (233). These include several parameters of the adaptive immune response, the so-called "immune risk phenotype" (IRP) as well as assessment of NK cell markers and functions. IRP is used as a predictor of mortality in the elderly people (234). One idea that has emerged is that a significant activity of the human immune system is progressively invested heavily to control cytomegalovirus (CMV) in aging which accounts for the higher systemic levels of inflammatory mediators (233). In fact, CMV infection makes a significant contribution to the IRP (231).

The precise mechanisms that lead to inflammaging have remained elusive and are poorly characterized. However, it is believed that the inflammation may be caused by a life-time exposure to clinical and sub-clinical infections, and non-infectious antigens (235). It has been suggested that chronic activation of immune cells, leads to remodeling of the immune system which favors induction of a chronic state of inflammation leading to tissue injury and pathology (235). Alternatively, the so-called “cellular exhaustion” as a result of reduced thymic output and T cell repertoire and concomitant increased oligoclonal expansion of memory and effector-memory cells contributes to inflammaging (236). Together, the inability to forcefully respond to novel pathogens as well as an increase in functionally distinct T-cell populations significantly prolongs infection, induces a pro-inflammatory phenotype and evokes a robust cytokine production in elderly population (237). The importance of the tissue injury that results from the chronic accumulation of polymorphonuclear neutrophils (PMN), their release of ROS and oxidative damage also appear to play a significant role in inflammaging (238).

The molecular inflammation hypothesis of the aging considers that the derangement in redox is the major factor for upregulation of NFKB, IL-1beta, IL-6, TNFα, cyclooxygenase-2, adhesion molecules, and inducible NO synthase and increased risk for age-related inflammation (239). The term “senoinflammation” is applied to the emergence of pro-inflammatory senescence-associated secret-ome, inflammasome, ER stress, Toll-like receptors (TLR)s, and microRNAs in aging tissues. The activators of seno-inflammation, the redox-sensitive core transcription factor NFKB, polarized macrophages, and a host of miRNAs are metabolically linked to the pro-inflammatory processes such as ER stress and autophagic activity (240). Single cell transcriptomics in aging rats showed that aging leads to the infiltration of aged tissues by neutrophils and by the macrophages that attain a pro-inflammatory (M1) state (241). M1/M2 macrophage activation occurs in a wide number of age related diseases including obesity, atherosclerosis or pulmonary fibrosis (242). However, CR blocks such responses and promotes the anti-inflammatory M2 profile in macrophages (241).

A complex array of inter-related genetic, environmental and age-related factors appear to account for the vulnerability or resilience of people to inflammaging. These factors include, but are not limited to, the responsiveness of promoter regions of

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cytokines, cytokine receptors and antagonists, age-related decreases in autophagy and obesity (243). The inflammatory signals include damaged molecules (self garbage), an array of nDNA, mtDNA, and miRNA that are encompassed in extracellular vesicles that freely enter the bloodstream. Continuous activation of macrophages by these damaged molecules (GarbAging) ultimately exhausts their ability to clear them and that surface receptors of macrophages sense the mis-placed self molecules and activate the inflammaging by activation of inflammasome (133). NLRP3 inflammasome is comprised of an intracellular multi-protein complex that recognizes pathogen-associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMP), which when activated, it leads to the release of IL-1β as well as IL-18 (244). The NLRP3 inflammasome is activated in age related disorders including obesity, insulin resistance, and inflammation (245-246). Another factor involved in aging is the failure to remove the host of cell debris and damaged organelles, by autophagy or mitophagy due to a progressive failure of proteasome.

Aging is associated with the release of a large number of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-12, IL-15, IL-18, IL-22, IL-23, TNF-α, and IFN-γ in aged tissues that likely contribute to aging pathologies (227, 247-249). The inflammatory response is initiated by inflammasome, cytosolic multi-protein oligomers that are required and activate the inflammatory responses of cells of the innate immune system, and is significant in protection against pathogens and in recovery from injury. Inflammasome leads to the proteolytic cleavage, maturation and release of pro-inflammatory cytokines. The inflammasome can lead to the oxidative stress that occurs with aging and to a form of programmed cell death related to the inflammatory response, known as pyroptosis (250). The inflammasome proteins including NLRC4, caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and IL-18 are shown to be elevated in the cytosol of cortical lysates in aged mice (251). The nucleotide metabolites have been shown to activate the NLRC4 inflammasome in old individuals (252).

The canonical Nlrp3 inflammasome controls a systemic low grade age-related 'sterile' inflammation in both periphery and brain that appears to be independent from the non-canonical caspase-11 inflammasome. Nlrp3 knockout has been shown to protect mice from age-related increases in the innate immune activation, alterations in CNS transcriptome and astrogliosis. Thus, Nlrp3 appears to link the systemic low grade inflammation to a significant functional decline that is observed in aging.

Progressive decrease in subcutaneous tissues and loss of muscle mass (sarcopenia) during aging are associated with sequential increase in fat that is deposited in viscera, or infiltrates major organs including liver, bone and muscle. These fat depots are not inert and they act as an endocrine or paracrine organ by release of hundreds of adipokines, and pro-inflammatory peptides (253-256). For example, leptin, which has a primary role in energy homeostasis, leads to the release of a number of proinflammatory cytokines, including TNF and IL-6, stimulates differentiation of monocytes into macrophages, and activates NK-lymphocytes (256). On the other hand, declining levels of adrenal steroid dehydroepiandrosterone (DHEA) and anti-inflammaging strategies such as higher levels of cortisol, as a result of upregulation of the hypothalamic-pituitary axis in response to inflammaging, appear to exert an adverse effect in aging population (243). Long lived individuals and centenarians have developed anti-inflammaging strategies that oppose the adverse consequences of sub-clinical tissue inflammation (227).

An arsenal of different approaches including cytokine therapy, hormonal replacement, anti-oxidant supplementation, and caloric restriction have all been proposed for attenuating or potentially reversing immunosenescence (257).

3.12. Stem cell exhaustion

Other than long lived cells such as neurons and myofibers, all the cells in the body are subject to wear and tear and must be replaced periodically to maintain the normal function and physiology of tissues and organs (258-260). This task is assigned to the adult stem cells, such as hematopoietic stem cells (HSCs), intestinal stem cells (ISCs),

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mesenchymal stem cells (MSCs), neural stem cells (NSCs), muscle stem cells (MuSCs), hair follicle stem cells (HFSCs) and germinal stem cells (GSCs) and satellite cells that maintain tissue regeneration and homeostasis (261-266). Therefore, the decline in stem cell number or function, the so-called stem cell exhaustion, is an important driver of aging (267). For example, consistent with a general decline in cell-cycle activity, HSCs show reduced cell division in aged mice (268). Also, age-associated decline in the differentiation of HSC populations generates fewer adaptive immune cells and leads to anemia in aged organisms (269). Defects in cell-cycle by DNA damage or chromosome disorganization also significantly and adversely reduce the functional activity of HSCs, and decreases blood production in aged organisms (270). Like other aged cells, aging population of stem cells with declined function, show evidence of age related DNA damage and exhibit an increased levels of *p16*INK4a (271-272). Accelerated proliferation in stem cells, for example, by *p21* prematurely exhausts the population of HSCs and NSCs (273-274).

In recent years, many causes of stem cell exhaustion have been defined. Stem cells appear to be under the control of the same signaling pathways that are disturbed by aging and those that can manipulate aging such as nutrient sensing pathways, telomere attrition, oxidative and mitochondrial damage, and genetic and epigenetic modulators of aging (275-281). One of the critical cause of stem cell exhaustion is aberrant nutrient signaling since it is known that Calorie Restriction (CR), Dietary Restriction (DR) and pharmacological manipulations of metabolic pathways that slow the metabolism and modify the epigenetic landscape can extend life-span whereas enhanced anabolic signaling and obesity have a reverse consequence (282-285). It has been shown that DR promotes the proliferation of ISCs through the nutrient signaling, mTORC1 and Sirtuin 1 (SIRT1), whereas rapamycin that inhibits mTOR prevents the exhaustion of these stem cells (286).

Other types of stem cell exhaustion have been attributed to the impaired autophagy that normally preserves quiescence and stemness and prevents stem cell senescence (287). For example, impaired autophagy leads to an imbalance in proteostasis, causes mitochondrial dysfunction, ramps up oxidative stress and causes satellite cells to senesce (288). SIRT1 which also regulates autophagy, is required for activation of MuSC that normally sustain a quiescent state (289). Conversely, the transcription factor, FOXO3, plays an important role in maintaining the quiescent state of NSCs and MuSCs, and is known to induce autophagy in HSCs under conditions of starvation by regulating genes involved in autophagy (290-294). Also, mTOR signaling which activates quiescent MuSCs and HSCs in nutrient-rich environments, is known to suppress autophagy and to limit life-span (295-297). Thus, it appears that autophagy is involved in stem cell aging by coordinately impacting their metabolism and epigenetic changes.

Stem cells express telomerase, yet, the telomeres of HSCs, NSCs, HFSCs and GSCs have been shown to shorten with aging (298-299). However, the real impact of telomere shortening in stem cells is not yet clear since mice that lack telomerase RNA component, *TERC*, fail to show any specific phenotype for three generations, and only in the fourth generation, they start to exhibit aberrant HSC lineage potential and stem cell exhaustion emerges only in their sixth generation (300-301).

The metabolome has an intimate link to epigenetic modifiers since it is, by now, clear that the metabolites derived from cellular metabolism can act as co-factors of epigenetic enzymes that induce chromatin modifications such as methylation or demethylation of histones or DNA or acetylation and deacetylation of histones (285). Thus, metabolism is one of most influential driving force that shapes the epigenetic landscape and provides the opportunity to use such co-factors as potential targets to reverse the aging epigenome including those in stem cells, to preserve their function and to prevent their senescence. It is also becoming increasingly clear that health-span and life-span and maintenance of stem cell populations are subject to modulation by regulators of nutrient sensing and cellular metabolism such as mTOR and insulin-FOXO pathways as well as by regulation of enzymes such as sirtuins, that utilize metabolites such as NAD^+, which is known to be capable in changing the global

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levels of histone acetylation (302-304). For example, NAD^+ has been shown to be involved in the activation of murine MuSC by switching, from fatty acid oxidation in quiescent cells, to glycolysis via an increase in the overall acetylation levels of H4K16 (305). Knockdown of phosphoserine aminotransferase 1 (*Psat1*) affects ESC differentiation by changing the levels of the metabolite, α-ketoglutarate (306). Besides NAD^+ and α-ketoglutarate, another metabolite involved in murine threonine metabolism, S-adenosyl methionine (SAM), induces age-related alterations of H3K4 methylation by acting as a co-factor for histone methyltransferases (307-308).

The epigenetic fate of MuSCs appears to be under the regulation of Sirt1 that senses the cellular energetic state via NAD^+ (266). Moreover, in-activation of Sirt1 leads to the abnormal expression of genes involved in amino acid metabolism, and a coordinate abnormal expansion of oligodendrocyte progenitors in mouse NSCs (309). On the other hand, Sirt6 deficiency, has been shown to impair the transcription of target genes of the anti-oxidant Nrf2 pathway, which is vital to the metabolic systems for modulating redox homeostasis. These transcriptions can be halted by the H3K56 acetylation, which in turn, appears to be sufficient to derail the normal redox homeostasis, leading to the senescence of human MSCs (310). Among the sirtuin members, Sirt7 is downregulated with age. This sirtuin, which modulates UPR^{mt} in response to the mitochondrial stresses, has been shown to be required for the maintenance of homeostasis of HSCs, partially by acting as a repressor of genomic targets of Nrf1 (311).

Age related pathologies such as Parkinson's disease (PD) lead to the exhaustion of NSCs, defects in neuronal differentiation and DNA repair (312). The induction of stem cell rejuvenation *in vivo* in age associated phenotypes has lent support for the concept that stem cell exhaustion is one of the hallmarks of aging (313-315). Thus, understanding the mechanisms that drive stem cell aging and decline in their ability to regenerate tissues is of great significance to remedy the age related pathologies and tissue atrophy which is one of the cardinal features of aged tissues. *In vivo* stem cell rejuvenation, has been offered as a significant recipe and as one of the anti-aging intervention at least for the reversal of some of the aging phenotypes (313).

Stem cell exhaustion is also frequently observed in genetic diseases that shorten life-span and increase the mortality in individuals with Hutchinson-Gilford progeria syndrome (HGPS), Werner syndrome (WS), and Fanconi anemia (FA) (316-319). Premature aging in WRN has been attributed to the exhaustion of MSCs as a result of genome instability due to the deficiency of the DNA helicase and WRN protein (315, 320-321).

3.13. NutrimiRAging

The nutrient sensing, which is regulated by multiple pathways including insulin/IGF-1 (IIS), PI3K, AKT, mTOR, AMPK, Sirtuin and PGC1α, appears to be deregulated in aging, providing a strong link between diet and aging. The fact that life can be extended by alterations of the diet and that calorie, diet and protein restrictions can extend the life-span, in diverse organisms, have strengthened the notion that aging results from insults mediated by the total calorie intake and the composition of the diet. The idea, that the metabolic rate and aging are intimately intertwined, emerged from observations, that reducing the metabolism by lowering the ambient temperature in worms and flies or reducing nutrients by limiting glucose in the culture media of yeasts, leads to life-extension (322). These and other similar observations placed mitochondria as well as nutrition at the forefront of forces that drive aging.

Glucose, amino acids and fatty acids are the main fuel sources that drive energy production by conversion of ADP to ATP and for fulfilling the cellular need for NAD^+. Each of the fuels require specific enzymatic and metabolic pathways and drive specific expression and utilization of surface receptors and nuclear transcription of members of the metabolic machinery. Cells have developed a complex array of signaling systems that respond to the fuel needs and sense the requirement of cells for gene expression, protein synthesis, growth, repairs and other

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functions. The nutritional sensing pathways that respond to dietary nutrients, degrade with age and lose their effectiveness, hence, leading to the idea that de-regulated nutritional sensing leads to loss of healthy aging and age related pathologies. The dietary restriction of nutrients, has been shown to extend life-span in *C. elegans* to *Drosophila* and mammals, leaving no doubt that life-span can be modified by reducing the total calorie intake and by restricting food and proteins particularly, sulfur containing amino acids. It is by now considered that the trans-sulfuration pathways including hydorgen sulfide (H_2S) tie the nutrition and nutrient-sensitive signaling to a healthy life-span (323-325).

3.14. miRagings

miRagings are the RNA sequences that impact aging through nutrient sensing pathways, as well as those that their expression changes with diet and aging. Also included are those that inhibit target genes linked to cell proliferation, apoptosis or metabolism, or play a role in the epigenetic regulation of gene expression or biological processes that are linked to aging (326-329). These RNAs include microRNAs (miRNA) and non-coding RNAs of about 22 nucleotides that reside within intra- or inter-regions of protein coding genes. Some of these RNAs are released into plasma and body fluids such as urine and cerebrospinal fluid, that due to the necessity of being protected from RNAses and degradation, are usually associated with lipoproteins or protein complexes or are present within exosomes (330).

Circulating miRNAs are potential biomarkers of health and might be useful to discriminate healthy from abnormal aging. The circulating levels of these group of miRNAs also changes with nutritional status and by age, potentially, by upregulation of p53 which can impact the Drosha complex and miRNA maturation (331-332). Expression profile of microRNAs in centenarians were more similar to those of young adults than those of octogenarians (80-89 years of age) suggesting that their expression level might be useful in predicting longevity (332). Expression of miRNAs namely, let-7 family, miR-33, miR-103, miR-107 and miR-29 which modulate insulin signaling pathway also changes by age related pathologies including type 2 diabetes (331-338). There are a class of miRNAs that are regulated by the pathways that are known to be involved in aging. Among these, miR-124a, which is involved in glucose-induced insulin secretion, is under the direct modulation of *AKT3* and *FOXA2* and, potentially, *SIRT1*. The IGF1/PI3K/AKT/MTOR pathway is regulated by let-7 expression, a microRNA that targets multiple components of the IGF1 pathway and mTOR (339). Other miRNAs such as miR-208a and miR-133a are overexpressed after an acute myocardial infarction, and circulating miR-423-5p is upregulated in heart failure (340-342). The expression of miR-146, miR-155 and miR-21 is changed by inflammation, a typical feature of aging and miR-155 and miR- are upregulated in B-cells of elderly (343-344). Despite the wealth of knowledge that aging changes the expression of many of known miRNAs, their direct impact and relevance in aging and age related disorders is still poorly understood (267).

3.15. Other theories of aging

There are a large number of theories that have attempted to explain aging. However, many theories have failed to adequately address all aspects of aging. This includes programmed theory, that argues that aging follows a pre-determined timetable, and others that posit that aging is due to a life-time accumulation of environmentally induced damage (345). The programmed theories are sub-divided into programmed longevity due to alteration of gene expression and senescence, endocrine or reproductive-cell cycle theories that maintain that aging is hormonally regulated, and immunological theory that describes aging to be attributable to immunological decline. The damage theory is sub-divided into wear and tear theory, rate of living theory, cross linking theory, and free radical theory (9, 346-349). Dis-engagement and activity theories indicate that aging might be impacted by social engagement and physical activity. In contra-distinction, according to the quasi-programmed theory, aging is not programmed, but rather is a consequence of genetic programs that determine, developmental growth, early in life (350-352).

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There are two highly repetitive regions in the genome, namely the telomeres and rRNA genes (rDNA). The finding that stability within rDNA regulates life-span led to the rDNA theory of aging. Recent studies have confirmed that the rDNA copy andthe stability of the repeats play a critical role in the control of aging and cellular senescence (353). Recently, it was shown that tissue-specific methylation of rDNA promoter strongly correlates with a lower expression of rRNA (354). We showed that replicative senescence leads to reduced levels of 18S, 5.8S and 28S rRNA, in replicative senescence and that promoter region of rRNA is hypermethylated, features that do not exist in DNA damage induced senescence (355).

Moreover, Cairns proposed the so-called “immortal DNA strand hypothesis” that hypothesizes that there are mechanisms that maintain the genome stability in stem cells that undergo rapid cell divisions to maintain tissue homeostasis (356). The stem cells divide asymmetrically giving rise to a new daughter cell that harbors the old organelles and mis-folded proteins and a younger self-renewed stem cell that retains the healthy parts of the original cell. However, the asymmetric segregation of DNA remained controversial and some suggested that random segregation occur in stem cells. However, there are some evidence that lend support for this theory in tissues such as fly male germline cells and in mouse hematopoietic system, mammary tissue, intestinal epithelium, skeletal muscle, and hair follicle (357-363).

4. CONCLUSIONS

Aging occurs in a progressive and sustained manner in all humans. Aging leads to a significant morbidity and mortality towards the end of life and exerts a significant burden to the society and to the world’s economy. Therefore, prevention or reversal of aging, is of paramount importance to all humans and eradication of aging, would undoubtedly lead to more prosperous societies across the globe. Throughout the past few decades, numerous hypotheses have been offered that all show that aging is associated with gradual and progressive decline in cell functions that arise as a result of damage to cellular compartments, organelles and bio-informational molecules. However, these cell-centric hypotheses fail to account for all the hallmarks of aging and currently, the most proximal cause of the cellular damage have remained elusive (1, 185, 236, 267, 277, 315, 321).

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Abbreviations: Deoxyribonucleic acid (DNA), Mitochondria DNA (mDNA), Nuclear DNA (nDNA), Ribonucleic acid (RNA), Ribosomal RNA (rRNA), Adenosine triphosphate (ATP), Electron transport chain (ETC), Superoxide dismutase (SOD), Reactive oxygen species (ROS), Heat shock protein (HSP), Base excision repair (BER), Nucleotide excision repair (NER), Double strand DNA breaks (DSB), Ultraviolet (UV), Hutchinson-Gilford progeria syndrome (HGPS), Ataxia-telangiectasia mutated (ATM), Werner syndrome (WS), Fanconi anemia (FA), Neonatal progeroid syndrome (NPS), Human mesenchymal stem cells (hMSCs), Induced pluripotent stem cells (iPSCs), mTOR complex (mTORC1), Tuberous sclerosis protein (TSC), Amyotrophic lateral sclerosis (ALS), Oxidative phosphorylation (OXPHOS), Mn superoxide dismutase (MnSOD), Non-homologous end-joining (NHEJ), Homologous recombination

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(HR), Mammalian nuclear factor-erythroid 2-p45 derived factor 2 (Nrf2), Skinhead family member 1 (SKN-1), NAD(P)H:quinone oxidoreductase-1 (NQO1), Heme oxygenase 1 (HO-1), Glutathione S-transferase (GST), Glutamate cysteine ligase catalytic subunit (GCLC), Cystine/glutamate (xCT) Transporter, antioxidant/electrophilic response element-mediated (ARE/EpRE), Unfolded protein response (UPRmt), Reverse transcriptase, Telomerase (TERT), Dyskerin (DKC), Senescence-Associated Secretory Phenotype (SASP), Cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), DNA damage response (DDR), Tumor necrossis factor (TNF), Interleukin (IL), Cytomegalovirus (CMV), Immune risk phenotype (IRP), Polymorphonuclear neutrophils (PMN), Endoplasmic reticulum (ER), Toll-like receptors (TLR), Damage associated molecular patterns (DAMP), Caspase recruitment domain (ASC), Dehydroepiandrosterone (DHEA), Hematopoietic stem cells (HSCs), Intestinal stem cells (ISCs), Mesenchymal stem cells (MSCs), Neural stem cells (NSCs), Muscle stem cells (MuSCs), Hair follicle stem cells (HFSCs), Germinal stem cells (GSCs), Sirtuin (SIRT), Phosphoserine aminotransferase 1 (Psat1), Nicotinamide adenine dinucleotide (NAD), Parkinson's disease (PD), Insulin/IGF-1 (IIS), Hydorgen sulfide (H_2S), Dietary restriction (DR), Calorie restriction (CR), Pathogen-associated molecular patterns (PAMPs), Damage associated molecular patterns (DAMP), S-adenosyl methionine (SAM)

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