Chapter 13
Metabolic Biomarkers in Aging and Anti-Aging Research

Paul C. Guest

1 Introduction

Human life expectancy has increased by approximately two-fold over the last 200 years, which has resulted in a significant increase in the proportion of elderly individuals in the population [1]. This increase in lifespan has been predicted to continue rising to reach an anticipated life expectancy of more than 85 years by the year 2030 for people in the developed world [2]. However, it comes as no surprise that advanced age is associated with a decline in physiological status, leading to an increase in age-related diseases [3]. Thus, the increase in life span is significantly associated with increased prevalence of diseases such as diabetes, metabolic disorders, cardiovascular disorders, cancer and neurodegenerative disorders [4]. Reducing the negative impacts of advanced age and increasing the human healthspan has therefore been an important goal of aging and anti-aging research throughout the world [5–7]. With this in mind, we are now beginning to understand the physiological mechanisms underlying aging and the next steps will be to identify and validate biomarkers and to target the underlying cellular and molecular determinants.

Aging can be defined as the time-dependent malfunctioning of molecular and physiological mechanisms in organisms, causing defects such as shortening of telomeres and increased production of damaging reactive oxygen species (ROS), which lead to increased senescence of cells and deterioration of the tissues as well as of the entire organism. Cellular senescence is one process by which cells cease to divide and this is thought to contribute to both tissue and organismal aging, and to be a

P. C. Guest (✉)
Laboratory of Neuroproteomics, Department of Biochemistry and Tissue Biology, Institute of Biology, University of Campinas (UNICAMP), Campinas, Brazil

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protective factor against cancer and tumor cell proliferation [8, 9]. Senescent cells have been found to accumulate in various tissues in mice in an age dependent manner [10]. The presence of these cells in tissues can cause dysfunction of the surrounding cells due to release of pro-inflammatory factors. Thus, aging is characterized by systemic degeneration over time and interventions that counteract this degeneration are expected to augment both the healthspan and the lifespan.

Several differing types of aging interventions have been tested in experimental models as a means of extending healthspan and for prevention or slowing of age-related diseases. For example, caloric restriction has been shown to decrease age-related diseases in nonhuman primates [11]. In addition, clinical trials of calorie restriction over a 2 year period found evidence of reduced oxidative damage, suggesting that this approach could also reduce the risk of age-related diseases in humans [12]. As we are now unravelling the mechanisms of how aging occurs, a number of compounds are currently undergoing testing for effectiveness in slowing the aging process in preclinical studies. This includes sirtuin activators [13], mammalian target of rapamycin (mTOR) inhibitors [14] and mitochondrial inhibitors [15].

The mitochondria are now known to be important in regulation of the aging process [16]. The primary function of these organelles is to generate energy for the organism in the form of adenosine triphosphate (ATP) but they are also involved in other physiological processes which have links to aging, such as apoptosis, autophagy and production of reactive oxygen species (ROS). Reduced mitochondrial function and generation of declining amounts of ATP have been observed in various organs and tissues, including skeletal muscle [17], heart [18] and brain [19]. This age-related mitochondrial impairment can be seen at multiple levels including mitochondrial number and morphology, electron transport chain (ETC) activity and ROS formation [20].

This chapter reviews how the complex process of aging may be regulated at the physiological, cellular and molecular levels and how this information is being unravelled by research using model organisms. At present, the most promising results have come from studies of the molecular pathways involved with caloric restriction, insulin/insulin-like growth factor signalling and mitochondrial ROS production, in nematode, fly and rodent models.

2 Biomarkers of Aging in Caenorhabditis elegans

C. elegans is a popular model organism for aging and anti-aging studies due to its short lifespan, fully annotated genome and age-dependent physiological changes [21]. Early research found that one gene associated with aging was *DAF-2*, which encodes a homologue of the mammalian insulin/insulin-like growth factor (IGF) family [22, 23]. Decreased DAF-2 signaling leads to translocation of the fork-head transcription factor DAF-16 into the nucleus, and this leads to activation of numerous genes associated with stress response, lipid metabolism, immunity and longevity

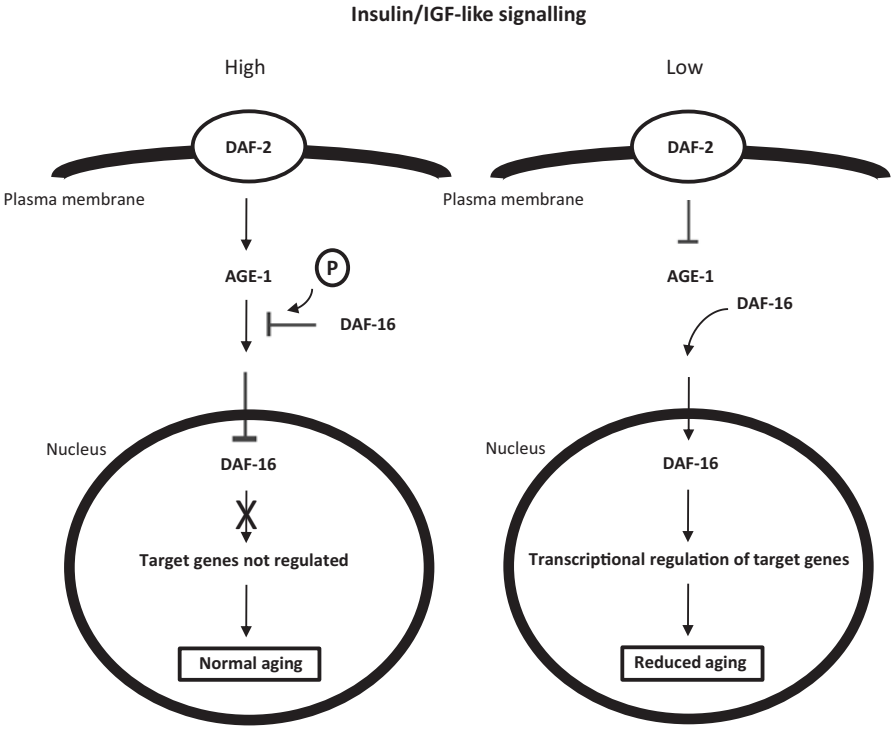

Fig. 13.1 Effects on aging via through the insulin/IGF-lik) in C. elegans. Under conditions of high levels of DAF-2 signalling, the transcription factor DAF-16 is phosphorylated and cannot enter the nucleus to activate target genes. Under conditions of low DAF-2 signalling, un-phosphorylated DAF-16 can enter the nucleus and turn on the target genes

(Fig. 13.1). The end result is a worm that can live twice as long as its natural counterparts [22]. There are also several models involving caloric restriction which lead to increased lifespan in C. elegans. EAT-2 mutant animals have dysfunctional pharynges, which results in decreased food intake along with a lifespan increase that is approximately 50% greater than wild type animals [24]. The effects of caloric restriction or impaired insulin/IGF-1-like signalling partially overlap in their downstream signalling processes, which include activation of pathways such as mitochondrial autophagy and inhibition of the mammalian target of rapamycin (mTOR) [23].

Other studies have linked caloric restriction to an improved oxidative stress response, which is mediated by the oxidoreductase enzyme thioredoxin 1 [25]. Another research group identified four genes that extend lifespan specifically in DAF-16 mutants but not in the EAT-2 mutants. These were the genes encoding S-adenosyl methionine synthetase (*SAMS*), Rab-like GTPase (*RAB-10*), dietary restriction response of unknown function (*DRR-1*) and a putative RNA-binding protein (*DRR-2*) [26].

As indicated above, the insulin/insulin-like growth factor-1 (ins/IGF-1) signalling pathway is involved in regulation of longevity and resistance to oxidative stress in C. elegans [27–29]. This is achieved via regulation of the downstream DAF-16 transcription factor [30, 31], which targets genes associated with these pathways during aging of long-lived C. elegans mutants (Fig. 13.1) [32, 33]. Under high insulin/IGF-like signalling conditions, such as following a meal high in fats and sugars, DAF-16 is phosphorylated and cannot enter the nucleus to activate target genes. Under conditions of low insulin/IGF-like signalling, un-phosphorylated DAF-16 can enter the nucleus and turn on the target genes. Intersetingly, a number of these studies have found increased ATP concentrations with reduced insulin/IGF-1 signalling and lower respiratory rates [34–38]. In addition, intracellular ROS are removed more efficiently under these conditions due to the higher activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase [34, 39].

The C. elegans life cycle consists of larval, dauer larval and adult stages. In the case of the dauer state, no feeding occurs [40, 41]. During the normal larval stages (L2-L4), cell growth and proliferation are driven by the tricarboxylic acid (TCA) cycle and young adult worms have a high tolerance to anoxia and protection against ROS [42, 43]. Significant decreases in oxygen consumption and metabolic rate have been seen in normal worms after these worms reach adulthood, consistent with decay in muscle function [44–46]. A recent study showed that expression of the cyclooxygenase (COX) assembly protein [mammalian gene homolog sco-1 (*SCO2*)] gene was increased with aging in wild type worms [47], suggesting that mitochondrial components are damaged by ROS during the aging process, inducing a shift from the TCA cycle to aerobic glycolysis. Conversely, the finding of an age-related increase in the levels of phosphoenolpyruvate carboxykinase (PEPCK) induced by calorie restriction in wild type C. elegans, indicates a shift in the balance to gluconeogenesis [47]. PEPCK plays an important role in energy production throughout various life stages of the worm and other invertebrates. The C. elegans PEPCK enzyme is involved in regulation of metabolism associated with cataplerosis, which is the removal of intermediate metabolites from gluconeogenesis and other pathways in anaerobic environments [48, 49]. Yanase et al. found that the upregulation of gluconeogenesis during aging in C. elegans was associated with reduced mitochondrial respiration and increased expression of PEPCK and the NAD-dependent protein deacetylase sir-2.1 [47, 50].

In C. elegans, exposure to the hyperoxia accelerates senescence so that the levels of intracellular ROS increase [51–53]. Mutations of the C. elegans *MEV-1* gene, encoding the large subunit of the cytochrome b succinate dehydrogenase, result in increased production of the mitochondrial superoxide anion (O2-), resulting in a shortened lifespan [54]. Likewise, the levels of cellular metabolites such as lactate and pyruvate are correlated with the switch from mitochondrial respiration to glycolysis during aging [47, 55]. These findings indicate that the cytochrome b succinate dehydrogenase plays an important role in energy metabolism as well as in superoxide anion production that is involved in sensitivity to atmospheric oxygen. Thus, further studies of the physiological and molecular changes in the *MEV-1* mutants might help to elucidate the pathological mechanisms of aging.

3 The Role of the Mitochondria in Aging

Mitochondria are the main site of energy production in most eukaryotic cells. This is where the processes of glycolysis and beta-oxidation of lipids occur in the process of generating ATP. This occurs via reduction–oxidation (redox) reactions along the oxidative phosphorylation (OXPHOS) complexes within the inner mitochondrial membrane (Fig. 13.2a) [56]. This is also one of the principal sites of aging as the progressive accumulation of cell damage has been proposed to be due to over-production of reactive oxygen species (ROS) (Fig. 13.2b) [57, 58]. Catalase is a peroxisomal enzyme which works together with mitochondrial glutathione peroxidise in antioxidant reactions preventing against ROS formation [59]. Studies in mice have shown that targeting of catalase to the mitochondria can result in reduced ROS damage and increased lifespan [60], along with an improvement in exercise performance [61]. With these results in mind, mitochondria-targeted catalase gene therapy has been proposed as a potential co-treatment approach in cases of Duchenne muscle dystrophy, in which the muscle tissues have high levels of ROS production [62]. This approach may also prove useful to slow the effects of sarcopenia, characterized by loss of muscle mass, which can occur during aging. Superoxide SOD2 is

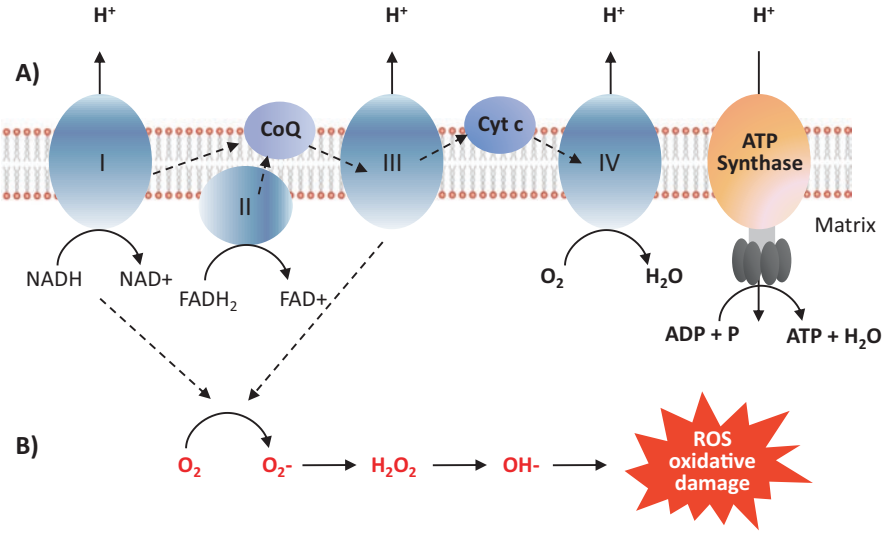

Fig. 13.2 (**a**) Generation of ATP via reduction–oxidation (redox) reactions along the oxidative phosphorylation (OXPHOS) complexes within the inner mitochondrial membrane. (**b**) Reactive oxygen species (ROS) production via the electron transport chain. Anions are produced at complexes I and III producing superoxide (O_2-). Hydrogen peroxide (H_2O_2) is converted into the hydroxyl radical (OH−). Superoxide and the hydroxyl radical are ROS that cause oxidative stress to macromolecules and organelles. Arrows with dashed lines indicate the direction of electron transfer. CoQ coenzyme Q, Cyt c cytochrome c, NAD+ oxidized nicotinamide adenine dinucleotide, NADH reduced nicotinamide adenine dinucleotide, FAD oxidized flavin adenine dinucleotide, $FADH_2$ reduced flavin adenine dinucleotide

a mitochondrial enzyme that converts superoxide species to H_2O_2 and O_2 [63]. In a heterozygous SOD2 ($SOD2^{+/-}$) knockout model, aged mice had significantly increased oxidative stress in their smooth muscle cells, resulting in a pathological stiffness, similar to that which occurs in atherosclerotic plaque formation during aging [64]. In a human study, suboptimal brain aging was found in subjects with a specific SOD2 variant [65]. These findings indicate an essential role of SOD2 in prevention against oxidative damage.

Coenzyme Q is a component of the mitochondrial electron transport that functions as an electron transporter between oxidative phosphorylation complexes, leading to ATP synthesis and it also serves as an antioxidant factor [66]. Given this, coenzyme Q supplementation has been tested with some success as a potential treatment of a number of disorders, such as cardiovascular disease, metabolic syndrome, neurodegenerative diseases and inflammation [67]. It has also been shown to prevent oxidative stress in a senescence-accelerated mouse model and in aged mice and rats [68, 69]. Along the same lines, the mitochondria-targeted form of coenzyme Q (MitoQ) was found to reduce cognitive decline, oxidative stress and loss of synapses in a mouse model of Alzheimer's disease [70] and to extend the lifespan of a C. elegans Alzheimer's disease model [71].

Caloric restriction appears to work by lowering mitochondrial O_2 consumption, leading to reduced generation of damaging ROS. This has been linked to changes in the mammalian target of rapamycin (mTOR) and sirtuin pathways [72]. Inhibition of mTOR has been found to extend lifespan in multiple species [73–76]. Sirt1 (the mammalian orthologue of Sir2) has been associated with neuroprotection [77], reduction of fat storage [78, 79] and insulin secretion from pancreatic-β cells [80]. Sirt1 increases expression of genes involved in fatty acid oxidation in response to low glucose, thereby providing a switch from glucose to a fatty acid oxidation metabolism under low caloric conditions [81, 82]. Some dietary activators of Sirt1 have been identified such as resveratrol and melatonin [83]. Another sirtuin family member (SIRT3) is thought to be involved in increasing the mitochondrial glutathione antioxidant defense system under caloric restriction conditions [84, 85]. One study of a mouse model lacking the p66 adapter protein found that the resulting increase in lifespan might be linked to improved metabolic homeostasis via regulation of Sirt3 activity [86]. Conversely, a Sirt3 knockout mouse ($Sirt3^{-/-}$) model showed increased oxidative stress and mitochondrial protein dysfunction [87].

Caloric restriction has also been shown to reduce the incidence of metabolic disease, cancer and brain atrophy, as well as all-cause mortality in non-human primate species [88, 89]. For example, a two- year caloric restriction study of healthy individuals found that this diet led to enhanced resting energy efficiency and lower systemic oxidative damage, compared to the effects seen for a control group on a normal caloric diet [12]. Another study of healthy elderly subjects found that a caloric restriction diet improved memory performance [90].

In summary, caloric restriction in a number of species has been shown to counteract age-related decline and increase lifespan by inducing a shift from carbohydrate to fatty acid metabolism, enhancing mitochondrial energy production and activating antioxidant defence mechanisms.

4 Redox Stress and Aging

The reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) is an essential component in the synthesis of fatty acids, cholesterol and deoxynucleotides as well as being a protective factor against redox stress. The levels of NADPH decrease with age [91, 92] due to oxidative stress resulting from the effects of accumulated mitochondrial electron transport chain dysfunction and inflammation [93, 94]. The mitochondrial theory of aging suggests that aging is associated with the accumulation of damage from increased mitochondrial ROS [58]. The redox theories of aging have proposed the idea that aging results from changes in the redox balance of molecules such as the oxidized and reduced forms of NADP (NADP+/NADPH) and glutathione (GSSG/GSH), as well as by changes in cell signalling [95, 96].

A number of studies have found that the rate of mitochondrial superoxide generation and phospholipid fatty acid saturation levels is negatively-correlated with lifespan in various species [97, 98]. The mitochondrial inner membrane is enriched in certain phospholipids essential for electron transport chain and ADP/ATP transport functions and these phospholipids are vulnerable to damage by ROS [99]. The loss of NAD+ and NADPH appears to be a factor in the aging of Drosophila melanogaster and C. Elegans [100, 101] and addition of NAD+ [102] or nicotinamide riboside [103] to the culture media has been found to extend lifespan. The decreased levels of NAD+ in aged mouse muscle leads to stabilization of the hypoxia inducible factor-1α (HIF-1α) and decreased c-Myc-induced expression of mitochondrial genes involved in electron transport chain function [104]. This leads to increased mitochondrial NADH and decreased NAD+ levels, as well as a reduction of the proton-motive force across the inner mitochondrial membrane. In turn, this would lead to decreased levels of glutathione reductase and, therefore, increased GSSG/GSH ratios. The increased oxidation within these pathways also results in oxidation of other redox-related molecules [105], thereby leading to oxidation of lipids, proteins and nucleic acids, culminating in the tissue dysfunction associated with the aging process.

Redox stress also appears to be associated with most age-related disorders such as diabetes and cardiovascular conditions. The NADP+/NADPH ratio is the strongest known redox determinant in age-induced oxidation with redox potentials ranging from −400 to −20 mV [106] and this ratio shifts to a more oxidized state with aging [107]. Quantification of oxidative stress in model systems can be performed by measurement of the GSSG/GSH ratio and the oxidation state can be determined in intact cells using the genetically encoded fluorescent probes, such as roGFP or roGFP2 [108]. However, these studies have demonstrated that both oxidizing and reducing changes can affect aging and longevity [109]. These findings suggest that redox measurements in the cytoplasm and mitochondria are important. In C. elegans, Reduced function of the NADPH-generating enzymes in C. elegans has been found to both increase and decrease longevity, most likely due to activation or inhibition of different compensation pathways. Reduction of the cytoplasmic NADP+/NADPH ratio has mostly resulted in increased longevity but this can also result in

reductive stress leading to mitochondrial oxidation and increased ROS generation. Thus, considerable further work is required in this area to fully elucidate the role of the redox potential in aging and longevity.

5 I'm Not Dead Yet (INDY)

INDY is a non-electrogenic solute transporter that transports di- and tri-carboxylates across the plasma membrane, as described in studies of D. melanogaster [110]. Reduced expression of INDY has been found to enhance longevity in a way that is similar to the effects of calorie restriction [111, 112]. Knockout of the mammalian homologue of INDY (the sodium-coupled citrate transporter; NaCT) led to protection from obesity and insulin resistance and this effect was found to be mediated by altered mitochondrial metabolism and reduced hepatic lipid generation [113]. Citrate is a vital metabolite that links multiple metabolic pathways such as glycolysis, gluconeogenesis and lipid synthesis [114–118]. Citrate is also an intermediate involved in the TCA pathway, which leads to generation of energy in the form of ATP. Transcription of INDY is regulated by the nutritional status. Calorie restriction was found to reduce expression of INDY in D. melanogaster [119, 120] and of the INDY homologue in mice [113]. On the other hand, administration of large amounts of olive oil increased INDY expression in rats [121]. Other studies have shown that regulation of INDY may occur via epigenetic mechanisms [122–124].

Mutations in the INDY gene are associated with lower levels of body fat, reduced circulating insulin-related proteins and decreased ROS and lifespan extension [111, 119, 125]. Genetic deletion or pharmacological inhibition of INDY in model organisms has been found to reduce the effects of a number of metabolic conditions such as non-alcoholic fatty liver disease (NAFLD), obesity and insulin resistance [113, 126–128]. For this reason, INDY is considered a potential drug target for metabolic diseases [129]. For example, it has been shown that knockdown of INDY expression using a liver-selective siRNA approach resulted in improved insulin sensitivity and reduced triglyceride accumulation [130]. Future studies are required to determine the effectiveness of INDY-directed compounds in the treatment of metabolic diseases and other diseases affected by metabolic disturbances including diabetes, obesity and cardiovascular disorders, as well as neurodegenerative and psychiatric disorders [131]. Ultimately, such compounds should be investigated to determine whether or not they promote healthier aging and increased longevity.

6 Obesity and Aging

Obesity has now become a global epidemic with a prevalence that has tripled over the last 30 years [132]. Obesity can increase the risk of numerous disorders such as diabetes, cardiovascular diseases and cancer, thereby increasing the mortality rate

[133–135]. To further our understanding of the effects of obesity, and to identify novel therapeutic approaches, a number of epidemiological approaches have been undertaken including population-based studies, case-control and clinical trials, which have to identification of risk factors, metabolic impacts and potential new treatments [136, 137]. However, such human-based studies are limited by factors such as underreporting and difficulty of discerning the impact of specific components of diets [138, 139]. As an alternative, animal-based studies can be more carefully controlled and these also allow the analysis of different tissues for determination of metabolic and molecular effects [140]. In addition, the pathways that regulate energy balance linked with weight control are highly conserved across the animal kingdom.

There are different types of high fat diets, such as those including 30–85% of the calories coming from fats [141], and these produce physiological effects such as obesity and insulin resistance [139, 142]. Weight gain is commonly used as a simple biomarker for monitoring the outcome of the diet or for determining the effects of an intervention, although body fat composition can give more precise information [139]. For example, one study found that administration of a 40% fat diet for 10 weeks caused rats to gain 10% in body weight but 35–40% in body fat [143]. In addition, the types of dietary fat can be important as several studies have now shown that lard-based diets are more obesogenic compared to oil-based diets [142, 144, 145].

Other studies have used a cafeteria-based diet approach as this closely mimics the "Western diet" [146]. Cafeteria-based foods include biscuits, cheese, processed meats, cakes, chocolate and peanut butter, as examples [147], which tend to induce hyperphagia [148, 149]. Therefore, compared with the high fat diet, the cafeteria diet can induce higher weight and abdominal fat gains, thereby inducing more damage to tissues such as the heart and liver, as well as leading to inflammation, hyperinsulinemia, hyperglycemia and glucose intolerance [150, 151]. Furthermore, a diet that combines both sugar and fats may be more efficient in eliciting metabolic changes and obesity in comparison to high fat diets [152]. The obesogenic effect of the high sugar/high fat diet may be due to the increased levels of saturated fatty acids that are less available as an energy source but instead are acetylated into triacylglycerol and stored in adipose tissue at increased levels [145, 153]. This is compounded by the insulinogenic effect of the rapidly absorbed simple sugars, resulting in a rapid decrease in blood sugar levels [154]. This triggers a neurochemical craving response similar to that seen in cases of addiction [155]. A model of the high sugar high fat diet which incorporates fructose and sweetened condensed milk as a source of sugar and beef tallow as a source of fat resulted in a greater body weight and abdominal fat gain, compared to controls along with induction of metabolic syndrome, and changes in the function of organs, such as heart, liver, and kidneys [156].

Taken together, these findings indicate that increasing our understanding of how obesity can alter cellular physiology and metabolic function could open new therapeutic avenues to extend the period of healthy aging.

7 Conclusions and Future Perspectives

Results from epidemiological studies have shown that most of the healthcare costs in developing countries are accounted for by age-related disorders and these costs are expected to increase along with the increasing proportion of the elderly population in developed countries. This is mainly due to the fact that the increase in average life expectancy has not been paralleled by a corresponding increase in healthspan [157]. Thus, considerable research has been underway to understand the process of healthy aging at the physiological and molecular levels. Results from preclinical models and data from human studies suggest that insulin/IGF signalling and efficiency of mitochondrial energy production are key regulators of this process. In addition, studies of these pathways have provided both rationales and potential drug targets for therapeutic interventions. A number of investigations along these lines have already been completed in animal models with the aim of finding a way of slowing the aging process and extending the human healthspan. Interventions such as caloric restriction and exercise, and administration of nutritional compounds and drugs such as antioxidants, omega-3 fatty acids, metformin and aspirin, target the mitochondria to delay or counteract the effects of aging [158]. Many of these approaches have shown early promise and have led to the identification of key biomarkers that can be used for monitoring the effects of aging as well as the efficacy of emerging anti-aging interventions. It is likely that such aging interventions will also delay the development of chronic diseases and thereby extend both the healthspan and the lifespan.

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