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Review Article

Diet and Aging

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Nutrition has important long-term consequences for health that are not only limited to the individual but can be passed on to the next generation. It can contribute to the development and progression of chronic diseases thus effecting life span. Caloric restriction (CR) can extend the average and maximum life span and delay the onset of age-associated changes in many organisms. CR elicits coordinated and adaptive stress responses at the cellular and whole-organism level by modulating epigenetic mechanisms (e.g., DNA methylation, posttranslational histone modifications), signaling pathways that regulate cell growth and aging (e.g., TOR, AMPK, p53, and FOXO), and cell-to-cell signaling molecules (e.g., adiponectin). The overall effect of these adaptive stress responses is an increased resistance to subsequent stress, thus delaying age-related changes and promoting longevity. In human, CR could delay many diseases associated with aging including cancer, diabetes, atherosclerosis, cardiovascular disease, and neurodegenerative diseases. As an alternative to CR, several CR mimetics have been tested on animals and humans. At present, the most promising alternatives to the use of CR in humans seem to be exercise, alone or in combination with reduced calorie intake, and the use of plant-derived polyphenol resveratrol as a food supplement.

1. Introduction

Nutrition has important long-term consequences for health. It is one of the lifestyle factors that contribute to the development and progression of chronic diseases including cardiovascular diseases, diabetes, and cancer [1]. The prevention or management of chronic diseases is a global priority since they account for more than half of the deaths worldwide [2]. The effects of nutrition on heath are not limited to the individual but can be passed on to the next generation. This observation has been confirmed by epidemiological studies and animal experiments. Epidemiologic observations linked smaller size or low weight at birth or during infancy to increased rates of coronary heart rate disease, type 2 diabetes mellitus, or adiposity in adult life [3–7]. In an animal model, for example, prenatal undernutrition reduced the offspring's life span [8] or lead to inadequate development of nephrons that increased the development of chronic kidney disease in later life [9].

2. Epigenetic Modifications by Dietary Factors

The effects of nutrition on the body are also mediated by epigenetic mechanisms [1]. The three known, closely interacting mechanisms are DNA methylation, histone modification, and noncoding microRNAs (miRNAs) as reviewed by McKay and Mathers [1]. Nutritional factors may induce epigenetic changes via three pathways: (a) a direct influence on gene expression, (b) activation of nuclear receptors by ligands, and (c) modification of membrane receptor signaling cascades [10]. Therefore, epigenetic mechanisms provide the organism with a robust, and time-responsive system for adapting gene expression that is (a) tissue-type specific, (b) appropriate for the developmental state of the organism, and (c) responsive to signals from the external and internal environment [1].

2.1. DNA Methylation by Diet. DNA methylation is tissue specific and is regulated by the enzyme DNA methyltransferase (DNMT) that modifies a cytosine base at the CpG dinucleotide residue with a methyl group to form 5-methylcytosine [11]. Examples of processes that are controlled by DNA methylation are X chromosome inactivation, imprinting, and silencing of germline-specific genes, carcinogenesis, and long-term memory formation [12]. Traditionally, DNA methylation was associated with suppression of gene expression. Thus, DNA methylation either physically impedes the binding of transcriptional proteins to the gene,

or the methylated DNA binds to proteins known as methyl-CpG-binding domain proteins that recruit additional proteins to the locus—such as histone deacetylases—that modify histones into compact, inactive chromatin as reviewed in [13, 14]. However, in some patients with cancer, both global DNA-hypomethylation and localized DNA-hypermethylation are present [15, 16].

Dietary constituents that are known to modulate DNA methylation are, for example, folate, vitamin B12, selenium, green tee polyphenols (e.g., epigallocatechin-3-gallate (EGCG), epicatechin, ganistein), and bioflavonoids (quercetin, fisetin and myricetin). Folate and vitamin B12 promote global DNA-methylation, whereas selenium, green tee polyphenols, and bioflavonoids reduce global DNA-methylation as reviewed in Davis et al. [17]. However, the local effect of these constituents on DNA methylation can differ from their global one. For example, long-term selenium consumption increases exon-specific DNA methylation of the p53 gene in rat liver and colon mucosa [18].

2.2. Histone Modification by Diet. Eukaryotic cell nuclei contain alkaline proteins (due to highly positively charged N-terminus with many lysine and arginine residues) called histones, that package and order the DNA into structural units called nucleosomes. Histones act as spools around which DNA winds and play a role in gene regulation, since genes that are active are less bound to histones; inactive genes are highly associated with histones [19]. The histones N-terminus (i.e., the histone tail) or the side chains at the globular histone core are the sites of epigenetic modifications [20].

Posttranslational modification of histones is significantly more diverse then DNA methylation. Some of the best understood histone modifications are methylation, acetylation, phosphorylation, ribosylation, ubiquitination, sumoylation, or biotinylation [20]. Examples of enzymes involved in posttranslational modification of histones are histone acetyltransferases (HATs), methyltransferases (HMTs), deacetylases (HDACs), and demethylases (HDMs). The effects of diet on histone posttranslational modification were recently reviewed by Link et al. [21]. For example, polyphenols from garlic or cinnamon inhibit HDAC; green tea polyphenols and copper inhibit HAT; EGCG inhibits HMT.

Histone methylation can modulate DNA methylation patterns, and DNA methylation might serve as a template for some histone modifications after DNA replication [20, 22]. It has been suggested that these interactions could be accomplished via direct interactions between histone and DNA methyltransferases [20, 22]. Such DNA-histone interactions could also be initiated or modulated by diet.

2.3. miRNA Modification by Diet. miRNAs are a family of approximately 22-nucleotides long noncoding RNAs in eukaryotic cells. miRNAs are posttranscriptional regulators and bind to complementary sequences on target messenger RNA transcripts (mRNAs) leading to posttranscriptional gene silencing due to mRNA translational repression or increased RNA degradation. However, miRNAs can also cause histone modification and DNA methylation of promoter sites thus regulating the expression of target genes by an alternative pathway. [23, 24]. The human genome encodes over 1000 miRNAs, which target more than 50% of mammalian genes in many human cell types [25–30]. Thus, miRNAs influence the expression of many transcription factors, receptors and transporters [31]. Recent evidence from experiments in human and in animal models suggests that nutrition (e.g., the consumption of fat, protein, alcohol or vitamin E) effects the expression of many miRNA [32].

Polyphenols (e.g., anthocyanin, curcumin and quercetin,) at nutritional doses modulate the expression of liver miRNA in mice *in vivo* [33]. Dietary modulation of miRNA expression could contribute to the cancer protective effects of genistein, curcumin, retinoic acid, or fish oil. Genistein (an isoflavone) inhibits uveal melanoma cell growth in a time and dose-related manner by inhibiting the of miRNA-27a expression [34]. Curcumin treatment upregulates miRNA-22 and downregulated miRNA-199a in a pancreatic cancer cell line [35] and also upregulates the expression of miRNA-15a and miRNA-16 in breast cancer cells [36]. Patients with acute promyelocytic leukemia that were successfully treated with chemotherapy and all-trans-retinoic acid had a downregulation of miRNA-181b and an upregulation of several miRNAs [37]. miRNA-10a downregulation, induced by treatment with retinoic acid, prevented pancreatic cancer metastasis in xenotransplantation experiments in zebrafish embryos [38]. Fish oil reduced the number of differentially expressed miRNAs in experimental animals and may be useful in prevention of colon carcinoma [39]. Indol-3-carbinol downregulated the expression of several miRNAs (i.e., miRNAs -21, -31, -130a, -146b and -377) in mice with induced mouse lung tumors [40]. Inadequate nutrition can also modulate miRNA expression. For example, dietary deficiency of folate was associated with significant overexpression of miRNA -222 in human with low folate intake [41]. Also, rats on a folate-methionine-choline deficient diet developed hepatocellular carcinoma with concurrent overexpression of miRNAs -17 to -92, -21, -23, -130, and -190 [42].

2.4. TOR Signaling Pathway and Nutrition. TOR (target of Rapamycin) is a protein kinase that functions as a central controller of cell growth and aging as reviewed elsewhere [43, 44]. Inactivation of the TOR signaling pathway promotes autophagy and prolongs life span [45]. Its function was first characterized in yeast but was also identified in other eukaryotes including mammals (hence mammalian TOR or mTOR). *In vivo*, mTOR exists in two multiprotein complexes, the mTORC1 and mTORC2. The mTORC1 functions as a nutrient-energy-redox sensor and modulates protein synthesis. Therefore, the upstream factors that stimulate the activity of this complex are insulin and other growth factors, amino acids (e.g., leucine), and stress (temperature change, caffeine, oxidative stress). Caffeine, hypoxia, and DNA damage inhibit mTORC1 activity. The upstream regulators of TORC1 activity are the AGC family of kinases (e.g., PKA; PKG and PKC) that are activated by phosphorylation [46]. In mammals, mTORC1 targets are S6 K1 and the eukaryotic initiation factor (4E-BP1) [47–52]. mTORC1-mediated phosphorylation of S6 K1 promotes protein synthesis and

4E-BP1 phosphorylation promotes localization of ribosomes to the cap structure of mRNAs. The phosphorylating activity of mTORC1 is regulated through its association with the RAPTOR (regulatory-associated protein of mTOR) protein [53, 54]. High nutrient or ATP levels activate mTORC1 by phosphorylating and thus inhibiting the TSC1-TSC2 complex as reviewed by Loewith and Hall [43]. This complex is a GTPase activating protein that modifies a second GTPase RHEB into a GTP bound state. RHEB, in the GTP bound state, directly binds and activates mTORC1 thus allowing mTORC1 to phosphorylate downstream targets [55]. Low cellular energy (high AMP levels) or low nutrient levels, in association with the tumor suppressor kinase LBK1, activate AMPK and an activated AMPK phosphorylates both TSC2 and RAPTOR thus inhibiting mTORC1 activity by two pathways [56]. In yeast, TORC1 promotes protein synthesis, ribosome biogenesis, regulates the relationship between cell cycle and cell size, promotes cell growth by inhibiting stress responses, stimulates autophagy, and regulates the signaling of mitochondrial dysfunction to the nucleus via the negative regulator of RTG1-dependent transcription [43, 44]. At the organ and whole body levels, the TORC1/S6 K1 signaling pathway regulates glucose homeostasis, insulin sensitivity, adipocyte metabolism, body mass and energy balance, tissue and organ size, learning, memory formation, and aging [57]. For example, the S6 K1 modulates the differentiation of mesenchymal stem cells into adipocytes. Overstimulation of the mTORC1/S6 K1 signaling pathway by excessive quantities of leucine in infant milk formulas could be the cause of increased adipogenesis and early childhood obesity [58].

The best understood functions of mTORC2 are the control of cell cycle-dependent polarization of actin cytoskeleton, endocytosis, and sphingolipid biosynthesis [43, 59, 60]. The upstream regulators of mTORC2 are insulin and IGF1 [44, 61]. The ribosome maturation factor Nip7 is required for mTORC2 kinase activity in yeast and mammalian cells [44, 61] and the substrates of mTORC2 are the AGC family of kinases including AKT, SGK1, and PKC [44, 62]. For example, mTORC2 promotes cell survival via AKT [63, 64] and also regulates hepatic glucose and lipid metabolism via insulin induced AKT signaling [62].

Although the signaling pathways of TORC1 and TORC2 are to some extent distinct they have a cooperative function to coordinate growth, mitosis, and cell size control. For example, TORC2 activates TORC1 via the AKT signaling pathway. TORC1 activation stimulates anabolic cellular pathways and TORC1 inhibition stimulates catabolic cellular pathways [65]. As a general rule, the sensitivity of the TORC1 and TORC2 signaling pathways could be not only cell-tissue specific but also TORC isoform dependent. For example, the activity of mTORC2 depends on the type of mammalian stress-activated protein kinase interacting protein (mSin1) isoform that constitutes this multiprotein-complex [66].

3. Nutrition and Aging

The possibility that mammalian life span could be significantly extended by diet modification was demonstrated in a rodent study published by McCay and coworkers. in 1935 [67]. Rats, as opposed to primates, have the ability to grow their entire life. One of the objects of this study was to determine the effect of retarding growth on the total length of life of rats of both sexes. Growth was retarded by limiting the intake of diet to the quantity necessary for maintaining the rats at fixed levels of body weights at the time of weaning or 2 weeks after weaning. At the same time, care was taken to provide adequate levels of all other diet constituents. Animals of both sexes, subject to diet restriction, had a prolonged total lenght of life. However, the effect of diet restriction on life span was more pronounced in male than in female rats [67]. In summary, this seminal experiment suggests that life span can be extended by diet restriction without malnutrition as opposed to diet restriction with malnutrition that can have an opposite effect as discussed elsewhere [1].

The standard protocol for studying the positive effects of a limited food intake is the use of caloric restriction, or calorie restriction (CR) diet that does not lead to malnutrition (due to lack of vitamins, minerals or essential biomolecules). CR means limiting calorie intake by 10–30% compared to the base line unrestricted intake for the studied life form and has been shown to improve health at all ages and also to slow the aging process in many eukaryotes [68]. The relevance of CR life span prolonging effects for primates was explored in a 20-year longitudinal adult-onset CR study in rhesus monkeys. The animals' baseline intake of calories was reduced progressively by 10% per month to a final 30% reduction that was maintained for the duration of the experiment. The effect of CR, compared to control, was evaluated by comparing the delay in mortality and the onset of some age-associated conditions most prevalent in humans (e.g., diabetes, cancer, cardiovascular disease, and brain atrophy). The conclusions of the study were that CR lowered the incidence of aging-related deaths (50% in control fed animals versus 20% in CR-fed animals) and also lowered the incidence of diabetes, cancer, cardiovascular disease, and brain atrophy [68].

4. Caloric Restriction Effects in Humans

The fundamental assumption, that caloric restriction can extend the average and maximum life span and delay the onset of age-associated changes, has been proven in many organisms from yeast, worms, and flies to mammals [69–71]. In higher mammals, CR delays many diseases associated with aging including cancer, diabetes, atherosclerosis, cardiovascular disease, and neurodegenerative diseases [68, 72–74]. The incidence of these diseases increases with age and they contribute significantly to mortality. Therefore, CR could increase life span by increasing the body's general state of health and providing a nonspecific, resistance to chronic diseases and metabolic derangements [68, 72–74]. However, the ultimate question, how does CR effect the human body, was studied in a limited number of experiments [73–93]. The study of CR effects on human longevity faces ethical and logistical challenges since the average life span is close to 80 years for the population in developed countries. Therefore, human studies are focused on measuring the CR-related changes that could slow the aging process and

the progression of chronic diseases thus increasing life span. The most convincing evidence that CR could have a positive effect in humans was provided by experiments by Fontana and coworkers, by the Comprehensive Assessment of Long-Term Effects of Reducing Calorie Intake (CALERIE Phase 1), and by data obtained on the members of the Caloric Restriction Society (as discussed below).

Fontana and coworkers evaluated the effect of a 6-year long CR diet on risk factors for atherosclerosis in adult male and female adults (age range 35–82 years) and compared them to age-matched healthy individuals on typical American diets (control group). The total serum cholesterol level and low-density lipoprotein (LDL) cholesterol levels, the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL), triglycerides, fasting glucose, fasting insulin, C-reactive protein (CRP), platelet-derived growth factor AB, and systolic and diastolic blood pressures were all markedly lower in the CR group. The HDL cholesterol was higher after CR. Medical records of individuals in the CR group indicated that, before they began CR, they had serum lipid-lipoprotein and blood pressure levels in the expected range for individuals on typical American diets, and similar to those of the comparison group. The conclusion of the study was that long-term CR can reduce the risk factors for atherosclerosis [74].

The effect of fat loss induced by either (a) a long-term 20% CR or (b) a 20% increased energy expenditure (IEE) by exercise on coronary heart disease (CHD) risk factors was evaluated in a one-year randomized, controlled trial on 48 nonobese male and female subjects. The CR or exercise induced reductions in body fat were quantitatively similar and were accompanied by similar reductions in most of the major CHD risk factors, including plasma LDL-cholesterol, total cholesterol/HDL ratio, and CRP concentrations. The authors concluded that long-term CR or IEE of the same magnitude lead to substantial and similar improvements in the major risk factors for CHD in normal-weight and overweight middle-aged adults [83].

The effects of a 1-year, 20% CR regime or 20% IEE by exercise, on the oxidative damage of DNA and RNA, was evaluated by white blood cell and urine analyses in normal-to-overweight adults. Both interventions significantly reduced oxidative damage to both DNA and RNA in white blood cells compared to baseline. However, urinary levels of DNA and RNA oxidation products did not differ from baseline values following either 1-year intervention program. The conclusion of the study was that either CR or IEE by exercise reduce systemic oxidative stress which is reflected in a decreased DNA or RNA oxidative damage [85].

CALERIE is a research program initiated by the National Institute on aging that involves three research centers. The Phase 1 of CALERIE included three pilot studies to determine whether long-term (6–12 months) effects of 20–25% CR in free-living, nonobese humans could be investigated and to evaluate the adaptive responses to CR. The conclusions of this randomized, controlled, clinical trial were that CR subjects had a lower body weight, a decreased whole body and visceral fat, a reduced activity energy expenditure, improved fasting insulin levels, improvements in cardiovascular disease markers (LDL, total cholesterol to HDL ratio, and CRP), and no change in bone density compared to controls [76, 77, 83, 86, 92]. The objective of the ongoing CALERIE Phase 2 is to test if 2 years sustained 25% CR of *ad libitum* energy intake, results in beneficial effects that would be similar to those observed in animal studies [91].

Members of the Caloric Restriction Society (CRS) restrict food intake with the expectation that this would delay the disease processes responsible for secondary aging and to slow the primary aging process. Compared to age-matched individuals eating typical American diets, CRS members (average age 50 ± 10 yr) had a lower body mass index, a reduced body fat, significantly lower values for total serum cholesterol, LDL cholesterol, total cholesterol/LDL, and higher HDL cholesterol. Also fasting plasma insulin and glucose values were significantly lower than in the age-matched control group. Left ventricular diastolic function in CRS members was similar to that of about 16 years younger individuals. Chronic inflammation was reduced by CR and this was reflected in significantly lower levels of plasma CRP and tumor necrosis factor alpha (TNFα) [74, 78, 84].

Aging is associated with a progressive reduction in heart-rate-variability (HRV)—a measure of declining autonomic function—and also a worse health outcome. The effect of a 30% CR on heart autonomic function was assessed by 24-hour monitoring of HRV in adults on self-imposed CR for 3 to 15 years and compared with an age-matched control eating a Western diet. The CR group had a significantly lower heart rate and significantly higher values for HRV. Also, HRV in the CR individuals was comparable to published norms for healthy individuals 20 years younger. The authors suggest that CR reset the balance between the sympathetic/parasympathetic modulation of heart frequency in favor of the parasympathetic drive thus increasing the circadian variability of heart rate [93].

5. Cellular Mechanisms of Caloric Restriction

Most age-related changes in gene expression are less then two folds and are tissue specific [94]. Yet despite tissue-specific differences in the effect of age on gene transcription, the rate of aging across tissues appears to be coordinated, suggesting a role for systemic factors in coordinating the aging process at a whole body level [95]. The most common age-related changes include increased expression of genes involved in inflammation and immune responses, and reduced expression of genes involved in mitochondrial (MTH) energy metabolism and CR prevents the majority of these age-associated changes in gene expression [96, 97]. CR is suggested to counteract the age-associated changes by modulating the mTOR signaling pathway, IGF1/insulin signaling, adiponectin expression, DNA methylation, and histone acetylation and deacetylation.

5.1. Adiponectin Secretion in Caloric Restriction. A consistent change during CR is a reduction in body fat (i.e., a reduction

in white adipose tissue). White adipose tissue is not only a storage site for lipids but has an important role in blood glucose homeostasis, immune, and inflammatory responses that are mediated by adipocyte-derived, cell-to-cell, signaling molecules adipokines (e.g., adiponectin) [98, 99]. Therefore, adipose tissue could be an important factor for aging and CR-related metabolic changes.

The secretion of adiponectin is increased by reduced calorie intake (e.g., CR) and reduced by both insulin and IGF1 that decrease its synthesis. Cross-sectional studies demonstrate a consistent inverse relationship between plasma insulin and adiponectin concentrations. An increase in adipocyte size will also reduce the secretion of adiponectin [100]. Adiponectin promotes fatty acid oxidation in adipose tissue and reduces lipid accumulation in other peripheral tissues [101]; CR is associated with increased levels of adiponectin [102]. In humans, this hormone suppresses metabolic derangements that may lead to *type 2 diabetes, obesity, atherosclerosis*, or *metabolic syndrome* [103–105]. Adiponectin regulates mitochondrial energy production via AMPK. AMPK has many functions, it up-regulates cellular uptake of glucose, β-oxidation of fatty acids, expression of glucose transporter 4 (GLUT4), and mitochondrial energy production. The enzyme has an "energy-sensing capability" and responds to fluctuations in the intracellular AMP/ATP ratio. For example, adiponectin treatment of human myotubes leads to an AMPK-dependent increase in MTH biogenesis and reduces reactive oxygen species (ROS) production [106]. AMPK regulates MTH energy production by activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) directly, or through the endothelial nitric oxide synthase (eNOS) and NAD-dependent-deacetylase sirtuin1 (i.e., SIRT1 or silent mating type information regulation 2 homolog 1) signaling pathway. Increased AMPK activity during CR has also a cardioprotective effect, which is abolished in transgenic adiponectin antisense mice or in mice treated with an AMPK inhibitor [102]. Increased AMPK activity also stimulates eNOS activity thus reducing the chances of cerebral ischemic injury [107]. Additional cardioprotective effects that are mediated by increased secretion of adiponectin during CR are (a) inhibition of TNFα release and (b) inhibition of synthesis of adhesion molecules in endothelial cells. The latter suppresses the attachment of monocytes to the endothelial cells and delays the progression of atherosclerosis. Adiponectin modulated inflammatory responses are due to inhibiting the secretion of TNFα (a cytokine involved in systemic inflammation) from monocyte/macrophages and foam cells [108–110]; this may explain the reduced plasma concentration of inflammatory protein CRP in humans subjected to CR.

5.2. Insulin/IGF1 Signaling in Caloric Restriction. Insulin resistance is a well-known age-related metabolic change in mammals that can be reversed by CR [94]. CR has been reported to reduce IGF1 blood levels in mice but not in humans [111, 112]. Insulin and IGF1 inhibit FOXOs (an O subclass of the forkhead family of transcription factors) by a signaling pathway that includes insulin receptor substrate proteins (IRS), 3-phosphoinositide-dependent protein kinase-1 (PDPK1), and phosphatidylinositol 3-kinase (PTDINS-3 K), thus translocating FOXOs from the nucleus. FOXOs regulate the rate of aging in response to dietary cues and the disregulation of this pathway in mammals is associated with obesity and insulin resistance [113]. In a cell-type-specific manner, mammalian FOXO factors control various cellular functions including apoptosis, cell cycle, differentiation, and the expression of genes involved in DNA repair and oxidative stress resistance. These functions are assumed to be the basis for FOXO's ability to control life span [114]. The actions of insulin/IGF1 signaling pathway on FOXO1a are mimicked by black tea polyphenols [113] and polymorphisms in the FOXO3a gene were associated with longevity in humans [115]. CR stimulates SIRT1-mediated deacetylation of the FOXO3a, preventing nuclear FOXO3a activity and inhibiting Rho-associated protein kinase-1 expression thus activating nonamyloidogenic α-secretase processing of APP and lowering Aβ generation. This reduced Aβ generation is associated with the prevention of Alzheimer's disease type amyloid neuropathology and spatial memory deterioration in a mouse model [114]. The positive effect of CR on the insulin/IGF1 signaling pathway was also associated with a reduction in ROS production in MTH [116].

5.3. mTOR Signaling Pathway in Caloric Restriction. The regulation of life span by the mTOR signaling pathway is not completely understood. However, recent experimental work implies that it plays an important role in the cell's aging process [44]. Inhibition of mTOR with rapamycin expands maximal and median life span in mice. This effect was observed even when the treatment was initiated late in life, corresponding roughly to an age of 60 years in humans [44, 117]. The above mentioned, rapamycin-mediated life extension was not associated with change in disease patterns or causes of death suggesting that rapamycin increases life span by slowing-down age-related tissue and organ degeneration [44, 117]. mTORC1 inhibition could prevent tissue degeneration and extend life span by improving stem cell function. For example, reducing mTORC1 signaling with rapamycin restores hematopoietic stem cells self-renewal and hematopoietic function, improves immunity, and increases life span in mice [118]. S6 K1 and 4E-BP1 were suggested as effectors of the mTORC1 signaling pathway that regulates the aging process. As reviewed in Kapahi et al., reduced S6 K1 activity increases life span in various species including in mice [119] and overexpression of 4E-BP1 extends life span under rich nutrient conditions by enhancing mitochondrial activity in flies [120].

mTORC1 could also influence life span through mechanisms that are not associated with modulation of protein synthesis; for example, stimulation of autophagy, as a consequence of mTORC1 inhibition, could promote longevity by stimulating degradation of aberrant proteins and damaged organelles that are accumulating over time and impairing cellular homeostasis [44]. An example how disregulation of mTORC1 activity can affect life span is seen in the liver

of old mice with impaired fasting-induced ketogenesis and increased mTORC1 activity [121]. This impaired ketogenesis limits the supply of available energy substrates to the peripheral tissues thus reducing the organism's chances of survival during food deprivation.

The age-related decline in MTH function is counteracted by CR that increases the transcription of nuclear-encoded genes involved in the electron transport system [69]. The effects of CR on MTH could also be mediated by the mTOR signaling pathway since mTOR is necessary for the maintenance of mitochondrial oxidative function [122]. Two, S6 K1 and 4E-BP1 independent, mTOR/MTH signaling pathways have been suggested: the TORC1-YY1-PGC-1α complex [122] demonstrated in a mouse model or the TORC1-regulated complex of BCL-XL and VDAC1 located at the mitochondrial outer membrane in a T-cell leukemic cell model [123].

5.4. DNA Methylation in Caloric Restriction. The aging process is associated with a progressively reduced cell homeostasis and altered gene expression [124]. Aging causes a significant change in the distribution of 5-methylcytosine (the product of DNA methylation) across the genome and a decrease in global genome DNA methylation [124–130]. However, the promoter regions of some specific genes tend to switch from unmethylated to methylated status, leading to gene silencing (e.g., promoters of tumor or aging-related genes, such as *RUNX3* and *TIG1* [129, 131]). In summary, the aging process is associated with globally decreased but locally increased DNA methylation [132]. CR is assumed to delay the aging process by reversing aging-related DNA methylation changes thus increasing genomic stability [133, 134]. For example, CR increased the methylation level of proto-oncogene *RAS* in a rat model when compared to *ad libitum* fed animals [135]. A hypermethylated gene promoter is often recognized by transcriptional repressor complexes, thus leading to silencing the expression of these oncogenes, which contributes to the cancer prevention effects of CR [132]. In an *in vitro* human cell model of CR, the E2F-1 binding site in the promoter of the $p16^{INK4\alpha}$ gene (a tumor suppressor and aging-associated gene) was hypermethylated. This DNA hypermethylation blocked access of E2F-1 (an active transcription factor of $p16^{INK4\alpha}$) to the $p16^{INK4\alpha}$ promoter, resulting in $p16^{INK4\alpha}$ downregulation, thus contributing to the CR induced life span extension [136].

Obesity is an important metabolic disorder in humans that is closely associated with recognized causes of accelerated aging and increased mortality such as diabetes, hypertension or cancer [137]. Therefore, the antiageing effects of CR should have an impact on the progression of obesity and are used in clinical weight control interventions [138]. The practice of CR by obese humans revealed that hypocaloric diets cause DNA methylation changes in specific loci *ATP10A*, *WT1*, and *TNF-α*, which could be used as early indicators of a response to CR [139–141]. Further CR studies in humans are necessary to characterize the pool of DNA methylation-controlled candidate genes that could be closely correlated with metabolic pathways [132].

5.5. Posttranslational Modification of Histones in Caloric Restriction

5.5.1. Histone Acetylation/Deacetylation. Histone modifications are associated with gene activation or gene repression. The combination of modifications within histone tails directly changes nucleosomes configuration switching chromatin to either a compacted (tight-close) or a relaxed configuration (loose-open) [142]. Therefore, histone modifications determine the (tight-close: loose-open) ratio of chromatin and thus the degree of gene activity within a certain DNA region. For example, a deacetylated histone lysine residue has the positive charge, which attracts the negatively charged DNA strands producing a compact chromatin state that is associated with transcriptional repression. Alternatively, histone acetylation removes the positive charge and results in an open chromatin structure, which promotes gene transcription [132]. HDAC activity is increased during CR, therefore, global deacetylation may be a protective mechanism against nutrition stress and may influence the aging processes [136]. For example, enhanced activity of HDAC1 on the promoter regions of the $p16^{INK4\alpha}$ and human telomerase reverse transcriptase (*hTERT*) genes, the former a tumor suppressor in many human cancers and the latter a key regulator of telomerase activity modified by aging regulation, leads to beneficial expression changes of these two genes and contributes to longevity under CR conditions [136, 143, 144].

Several HDAC families have been identified, including class III NAD^+-dependent HDACs like Sirtuin1. Sirtuin1 (SIRT1 in mammals), and its orthologs in other species (e.g., Sirtuin2 in yeast) are important for aging regulation and CR-related lifespan extension [145–149]. The enzymatic activity of SIRT1 depends on NAD^+/NADH ratio, a key indicator for oxygen consumption, thus suggesting that this protein is responsive to the metabolic state of cells. The role of SIRT1 in mediating CR and lifespan extension is supported by several animal models, human subjects, and *in vitro* CR cellular systems [136, 145, 146, 148–154]. CR induces SIRT1 expression in several tissues of mice or rats [146]. SIRT1 is assumed to mediate CR-induced metabolic alterations and subsequent aging retardation by (a) increasing stress resistance by negative regulation of p53 and FOXO [155–159] and (b) by initiating a series of endocrine responses, including inhibition of adipogenesis and insulin secretion in pancreatic β cells by regulation of key metabolism-associated genes such as peroxisome proliferator-activated receptor G coactivator 1α (PGC-1α) [160, 161]. Although SIRT1 is classified as an HDAC, it also deacetylates nonhistone substrates [146, 152] including key transcription factors (e.g., FOXO), regulatory proteins (e.g., p53, $p16^{INK4\alpha}$), and DNA repair proteins (e.g., Ku70) that are involved in lifespan extension by CR. For example, downregulation of p53 by SIRT1 deacetylation may affect lifespan by inhibiting cellular apoptosis and replicative senescence processes [155–157, 162–164]. FOXO protein can be directly deacetylated by SIRT1 at lysine residues and its expression is reduced, thereby repressing FOXO-mediated apoptosis [158, 159]. The DNA repair protein, Ku70, can become deacetylated by SIRT1, allowing it to inactivate

the proapoptotic factor BAX, thus inhibiting apoptosis [165, 166]. $p16^{INK4\alpha}$ is a cyclin-dependent kinase inhibitor, an important tumor suppressor protein and a potential aging biomarker since it is significantly accumulated during the aging processes [167–171]. CR-activated SIRT1 can directly bind to the $p16^{INK4\alpha}$ promoter and decrease its expression through a deacetylation effect, which contributes to delaying the aging process and to life span extension in human cells *in vitro* [153]. As stated previously, SIRT1 also regulates the expression of genes that are involved in metabolic pathways. PGC-1α is a key regulator of gluconeogenesis and fatty acid oxidation [160, 161] and is upregulated during CR by SIRT1-mediated deacetylation, which increases its ability to coactivate HNF4α, a transcription factor that promotes the expression of gluconeogenic genes and represses genes involved in glycolysis [147, 152]. In summary, SIRT1 plays an important role in the cross-talk between epigenetic and genetic pathways [132].

5.5.2. Histone Methylation. In contrast to histone acetylation, associated with open chromatin status and subsequent gene activation, differentially methylated forms of histones show unique association patterns with specific proteins that recognize these markers and thus lead to gene silencing or activation [132]. Histone lysine residues can be mono-, di-or, tri-methylated, leading to either activation or repression depending upon the particular lysine residue that is modified [172, 173]. For example, CR elicited histone methylation modifications such as di- or tri-methylated histone H3 at lysine residue 3 or 4 regulate expression of key aging-related genes, $p16^{INK4\alpha}$ and *hTERT*, thereby contributing to CR-induced lifespan extension of human cells [136, 153].

5.6. miRNA Expression in Caloric Restriction. miRNA expression patterns change with age; some miRNAs are downregulated and some are upregulated. Expression profile analysis of 800 miRNAs in human peripheral blood mononuclear cells revealed that the majority of miRNAs decreased in quantity including miRNAs involved in cancer development [174]. Since human tumors are often associated with a general downregulation of miRNAs, the reported age-related global decrease in miRNA could increase the frequency of cellular transformation and tumor genesis thus reducing life span. The decrease of these latter miRNAs with advanced age was also associated with an increased expression of target proteins phosphatidylinositol 3-kinase, stem cell factor receptor (c-KIT) and histone H2A [174]. Animal studies also support the role of miRNAs in aging. For example compared to wild-type controls, *C. elegans mutants* with deletion of miRNA-239 have a significantly prolonged lifespan and *C. elegans* mutants with deletions of miRNA-71, miRNA-238, and miRNA-246 have a significantly reduced lifespan [175]. The longevity of Ames dwarf mouse—attributed to their increased insulin sensitivity, increased stress resistance and reduced tumor frequency as a result of reduced IGF-1 activity—was associated with liver miRNA-27a suppression of regulatory proteins ornithine decarboxylase and spermidine synthase that occurred sooner in postnatal life that in wild-type mice [176].

CR changes miRNA expression profile. In mouse breast tissue, of animals restricted to 70% of normal diet for 6 months, CR increased the expression of miR-203 that targets caveolin-1 and p63 important factors affecting growth and invasive potential of cancer cells [177]. The authors concluded that CR could reduce the incidence, progression and metastasis of breast cancer thus contributing to an increased life span [177]. The brain of CR mice—after an 8-month reduction of calories to 60% of normal *ad libitum* intake—shows a decreased expression of miRNA-181a, miRNA-30e, and miRNA-34a with a concomitant increase in BCL2 expression and a concomitant decrease in BAX expression with reduced activities of Caspases 9 and -3. Decreased activities of Caspases 9 and 3 are associated with a reduced rate of apoptosis [178]. BAX and Caspase 3 activity is increased in Alzheimer's and Parkinson's disease; therefore, the progress of these common neurodegenerative diseases could be delayed by CR thus prolonging life span [179–183].

6. Mimetics of Caloric Restriction

Since long-term CR is necessary to produce beneficial effects on health and longevity observed in experimental conditions, alternatives have been investigated that could produce the positive effects of CR without food restriction. An ideal calorie restriction mimetic (CRM) should (a) elicit metabolic, hormonal and physiological effects similar to CR, (b) not require a significant reduction in long-term food intake, (c) activate stress response pathways similar to CR and (d) extend life span and reduce or delay the onset of age-related diseases [184]. To speedup the search for a candidate CRM the National Institute on Aging established the Interventions Testing Program as a multi-institutional program to test substances predicted to "extend lifespan and delay disease and dysfunction" [185–189].

6.1. Caloric Restriction Combined with Exercise. Male rats are the favorite animal model to study whether exercise in combination with CR (i.e., CE) potentiates the health-promoting benefits caused by CR alone, because these animals do not increase their caloric intake to compensate for their exercise-induced caloric expenditure [180]. Some studies concluded that CE does not have health-promoting benefits beyond those elicited by CR [111, 190–192]; there was no significant change in oxidative stress levels or pro-inflammatory protein levels in exercised animals fed an 80% CR diet [191, 192] and no effect on the animal's maximal life span [190]. On the other hand, CE reduced CRP levels to a greater extent than CR by itself [193] and reduced the chances of developing both myocardial necrosis and myocardial ischemia [194, 195].

Several human CE studies investigated the effect of a 25% total caloric reduction with 12.5% coming from exercise induced expenditure and another 12.5% coming from CR. The majority of them found no significant difference between CR and CE in respect to fasting insulin levels, DNA damage, muscle mitochondrial gene expression, triglyceride levels, and liver lipid content [76, 196–198]. The exceptions are two studies that reported a further reduction in both

diastolic blood pressure and LDL cholesterol when CR with exercise was compared to CR alone [198, 199]. Also, CE has been shown to increase bone mineral density at the femoral neck and reduce sTNFR1, an inflammatory biomarker, in overweight postmenopausal women [200]. The main advantage of combining CR with exercise over CR alone is that it may be easier for an individual to comply with a CE regimen where the total energy (i.e., caloric reduction) is divided between exercise-induced expenditure and calorie restriction [201].

6.2. Dietary Restriction. Dietary restriction (DR) refers to the modification of the quantity ratio between protein, fat, and carbohydrates with or without reducing the total intake of calories. Neither carbohydrate restriction nor lipid restriction are effective alternatives to CR and both failed to decrease reactive oxygen species production or oxidative DNA damage [202–208]. In an animal model, protein DR seems to be an alternative to CR. Protein DR was reported to increase the maximum lifespan in rodents by 20% [206]. The life-extending benefits of protein DR were attributed to a methionine restriction in diet [209–215]. For example, a 40% methionine restriction has been reported to decrease both mitochondrial reactive oxygen species generation and oxidative damage in mitochondrial DNA [216, 217]. Evidence that supports the link between methionine restriction and increased life span includes (a) inverse relationship between methionine content and maximum life span in mammals [218], (b) methionine supplementation increases LDL cholesterol oxidation [219] and (c) increased methionine intake increases plasma homocysteine concentrations, thus increasing the risk of cardiovascular disease and mortality [219]. Also, it has been demonstrated that a 40% restriction of all dietary amino acids except methionine failed to reduce both mitochondrial reactive oxygen species generation and oxidative damage in mitochondrial DNA [220]. In summary, animal experiments suggest that about half of the life extension effect of CR can be attributed to methionine restriction [206]. Therefore, further work in humans is justifiable since methionine DR is feasible and tolerable [221].

6.3. Alternate Day Fasting. Alternate day fasting (ADF) alternates 24-hour periods of *ad libitum* intake with partial or complete restriction of calorie intake. Therefore, ADF does not necessarily reduce overall caloric consumption or bodyweight, since subjects may compensate for the reduced caloric intake during fasting periods by overeating in the *ad libitum* intake period [222, 223]. ADF extended lifespan in animal trials [223–225]. Some authors attributed the increased life span during ADF to the concomitant increase in brain-derived neurotrophic factor [215]. ADF also attenuated or prevented the development of age-related disease processes, including cardiovascular disease, kidney disease, cancers, and diabetes [222, 223, 225–230]. Human trials have established the feasibility of ADF in humans [231]. The preliminary results of ADF-human trials [231–233] cannot be compared to CR-human trials since the ADF-trial periods ware relatively short (from a few days to 20 weeks) compared to the CR-trial periods (6 months to 6 years) [74, 83, 85]. However, even during such brief trial periods, some potentially beneficial effects were noted: a decrease in fasting insulin with no difference in fasting glucose [231] and an improved bronchial responsiveness to medication [233]. It has been reported that peripheral blood mononuclear cells of normal weight middle-age male and female subjects on a 2-month long ADF responded with a reduced capability to produce cytokines upon stimulation [234]. To date, there are no reports in regard to changes in biomarkers specific to blood lipids and oxidative stress in ADF subjects.

6.4. Resveratrol. Resveratrol (RSV), a plant-derived polyphenol in the skins of red grapes, is the most studied caloric restriction mimetic. RSV is reported to activate Sir2 (SIRT1 homolog) [235], thus mimicking the benefits of CR—without restricting calorie intake—such as increasing lifespan in yeast, worms, flies, and fish [235–238]. Recently, the assumption that activation of Sir2 by direct binding with RSV is responsible for extended lifespan has been challenged in experiments in multiple organisms [239–248]. For example, RSV is known to produce a wide array of effects in mammalian cells, including activation of AMP-activated protein kinase (AMPK) that is involved in some of the same pathways as SIRT1 and directly phosphorylates PGC-1α. [249, 250]. SIRT1 can activate the kinase upstream of AMPK, but this pathway does not appear to be necessary for AMPK stimulation by RSV [251]. Recently, it was reported that SIRT1 is essential for moderate doses of resveratrol to stimulate AMPK and improve mitochondrial function *in vitro* and *in vivo* [252].

Although the mechanism of RSV-mediated CR-like effects are not fully understood, it appears that RSV treatment produces a transcriptional response similar to CR [253], and in the presence of a high-fat diet, both health and longevity benefits have been reported with RSV use in a mouse model [249]. The beneficial effects of RSV use in obese mice were increased insulin sensitivity, improved motor coordination, and decreased incidence of cataracts [253, 254]. There was no significant life span increase in adult mice when RSV was added to a normal diet [254, 255]. This finding implies that RSV is not a true CRM [256]. A one-year treatment with RSV increased resting metabolic rate and total daily energy expenditure in nonhuman primate with any adverse health effects, implying that long-term use of RSV is effective and safe [257, 258]. CR, in the same animal model and experimental protocol, reduced total daily energy expenditure but did not change resting metabolic rate [258].

There have been only a few studies on RSV effects in humans, however the results are encouraging. The use of 0.1 mM RVS in cultures of human mesenchymal stem cells promotes cell regeneration by inhibiting cellular senescence; at higher concentrations (5 mM or more) RSV inhibits cell regeneration by increasing senescence rate, cell doubling time, and S-phase cell cycle arrest [259]. In human peritoneal mesothelial cells RSV delays replicative senescence by mobilization of antioxidative and DNA repair mechanisms

as measured by increased expression of proliferating cell nuclear antigen, augmented fraction of cells in the S phase of the cell cycle, increased number of divisions, diminished expression and activity of senescence-associated β-galactosidase, upregulated biogenesis of mitochondria, increased activity of superoxide dismutase and reduced DNA damage [260]. RSV and other polyphenols have low bioavailability in humans. However, RSV and its metabolites do accumulate within human cells *in vivo* in a tissue-specific and dose-dependent manner [261]. A six-week supplementation regime with RSV suppressed the binding of nuclear factor kappa B (NF-κB), decreased ROS generation, and decreased the levels of TNFα and interleukin-6 (IL-6) in mononuclear cells. The plasma levels of TNFα and CRP were significantly reduced as well. There were no significant changes in fasting plasma concentrations of cholesterol (total, LDL and HDL), triglycerides, or leptin in RSV-treated group compared to the control group of healthy individuals receiving placebo [262]. A high-fat, high-carbohydrate diet induces inflammation and oxidative stress [263]. Healthy humans on a high-fat, high-carbohydrate meal, taking a single-dose supplement of RSV and other grape polyphenols, had a significantly increased messenger RNA (mRNA) expression of the *NAD(P)H dehydrogenase [quinone] 1* and *glutathione S-transferase-p1* genes—implying a strong anti-oxidant effect. The single-dose RSV supplement also attenuated the meal-induced increase of plasma endotoxin and lipoprotein binding protein concentrations and attenuated the expression of $p47^{phox}$, TLR-4, CD14, SOCS-3, IL-1β, and KEAP-1 [264]. Therefore, RSV reduces the oxidative and inflammatory responses of a high-fat, high-carbohydrate meal, and it may reduce the risk of atherosclerosis and diabetes [261]. Preliminary results suggest that RSV also improves the glucose tolerance and insulin sensitivity [265]. The improved insulin sensitivity was attributed to decreased oxidative stress [265].

The causal association between red wine and grape juice consumption and the reduction of risk factors for cardiovascular disease (reduced blood flow, increased oxidative stress and inflammation) is well known [266–269]. RSV upregulates eNOS, thus promoting nitric oxide mediated vasodilatation and increased blood flow [270–272]. Also, RSV attenuates hemostasis-related activation of human platelets [273]. Increased arterial blood flow, after a single bolus of RSV, was measured in the brain and arm [274, 275]. However, increased brain blood flow after RSV treatment was not associated with an enhanced cognitive function [274].

Improved insulin resistance, arterial blood flow, and decreased oxidative stress and inflammation are associated with short-term use of RSV but there are no human data on the long-term health benefits [261]. In summary, further research is needed to clarify the biochemical pathways of RSV mediated effects and to establish its long-term effects in humans [276].

6.5. Rapamycin. Rapamycin (RAP) is an antibiotic and inhibitor of TOR (target of rapamycin) signaling in cells, with known immunosuppressive and antiproliferative effects [277]. TOR is a mediator of nutrient signaling in cells and is proposed to play a role in aging and the CR response (see Section 6.3). When RAP was administered to mice at about 20 months of age there was a significant, about 10% increase in mean life span extension in male and female mice. Since there were no significant changes in the organ pathology in the RAP feed mice, compared to control, the authors suggested that the longevity benefits of RAP could be at least partially mediated by biochemical pathways independent of the CR response [117]. The existence of multiple, RAP activated life-extension biochemical pathways were also suggested in flies. RAP feed adult drosophila had an increased life span. The suggested mechanism for this RAP increased longevity was by the TORC1 branch of the TOR pathway, with alterations to autophagy and translation. However, RAP could increase life span of weak insulin/IGF1 signaling pathway mutants and of flies with life span maximized by CR, suggesting additional mechanisms for life span extension [278]. Lifelong administration of rapamycin, administrated intermittently 2 weeks per month, extended lifespan in normal inbred female mice. Significantly, rapamycin inhibited age-related weight gain, decreased aging rate, increased life span and delayed spontaneous cancer [279]. Adult mice treated with rapamycin, starting at 2 months of age, perform significantly better on a task measuring spatial learning and memory compared to age-matched mice on the control diet. However, rapamycin did not improve cognition in adult mice with pre-existing, age-dependent learning and memory deficits. The rapamycin-mediated improvement in learning and memory was associated with a decrease in IL-1β levels and an increase in NMDA signaling. [280]. Since rapamycin is used as an immunosuppressive, its relevance for longevity in humans has yet to be established [117].

7. Diet and the Aging Population

An important demographic tendency in the developed world is a progressive increase in the percentage of the population over 65 years of age and a simultaneous decline in the percentage of the working age population. The health implications of these trends are a shift from acute to chronic and age related illnesses (e.g., Alzheimer's disease, osteoporosis, cardiovascular diseases, and cancer), increasing heath costs and an increasing economic burden to the society and to the individual [281–283]. Therefore, any dietary intervention that has the potential of delaying the progression of chronic and age-related illnesses could have a significant impact not only on the individual's quality of life but also on the society's ability to deal with the health and economic implications of an aging population. There is a body of data suggesting that CR significantly reduces the rate of age-related changes in humans [73–93]. However, there is no data that CR promotes longevity in humans. Studies of people with exceptional longevity suggest that a family history of longevity and of a low prevalence of age-related diseases enables a significantly prolonged life span even when the subjects were obese, smoked or did not exercise regularly. Therefore, exceptional longevity in humans could be more dependent on genetics than lifestyle [284–286].

8. Conclusions

Caloric restriction or calorie restriction mimetics elicit coordinated adaptive stress responses at the cellular and whole-organism level by modulating the signaling pathways of adiponectin, insulin/IGF1, AMPK, mTOR, FOXO, p53, and sirtuins [287]. Sirtuins could play an important role in the cross-talk between epigenetic and genetic pathways [132]. The activation of these adaptive stress responses may prevent the initiation of apoptosis by the intrinsic pathway [288]. Furthermore, it may stimulate autophagy to provide substrates for energy production and for the anabolic processes involved in cellular regeneration and synthesis of antioxidants and heat-shock proteins [287]. A large body of experimental evidence proves that the overall effect of these adaptive stress responses is an increased resistance to subsequent stress, thus delaying age related changes and promoting longevity. Therefore, CR, alone or in combination with caloric restriction mimetics, could improve the quality of life of the aging population.

Abbreviations

4E-BP1: Eukaryotic translation initiation factor 4E binding protein 1
ADF: Alternate day fasting
AGC: Acronym of the protein kinase A, G, and C families
AKT: Serine-threonine-specific proteinkinase also known as protein kinase B (PKB)
AMP: Adenosine monophosphate
AMPK: 5′ adenosine monophosphate-activated protein kinase
ATP: Adenosine-5′-triphosphate
ATP10A: Probable phospholipid-transporting ATPase VA also known as ATPase class V type 10A or aminophospholipid translocase VA gene
Aβ: Amyloid beta
B12 vitamin: Cobalamin
BAX: Bcl-2 associated X protein
BCL-XL: B-cell lymphoma-extra large, a transmembrane mitochondrial protein
CALERIE: Comprehensive Assessment of Long-Term Effects of Reducing Calorie Intake
CD14: Cluster of differentiation 14 protein also known as CD14 protein
CE: Exercise in combination with CR
CHD: Coronary heart disease
CpG dinucleotide: Cytosine-phosphate-guanine dinucleotide
CR: Caloric restriction or calorie restriction diet
CRM: Calorie restriction mimetic
CRP: C-reactive protein
CRS: Caloric Restriction Society
DNA: Deoxyribonucleic acid
DNMT: DNA methyltransferase
DR: Dietary restriction
E2F-1: Transcription factor E2F1 protein
EGCG: Epigallocatechin-3-gallate
eNOS: Endothelial nitric oxide synthase
FOXO: O subclass of the forkhead family of transcription factors; known FOXO family members are FOXO1, FOXO3, FOXO4 and FOXO6
GLUT4: Glucose transporter 4
GTP: Guanosine-5′-triphosphate
GTPase: Enzyme that hydrolyses GTP
HAT(s): Histone acetlytransferase(s)
HDAC(s): Histone deacetylase(s)
HDAC(s)s: Histone deacetylase(s)
HDL: High-density lipoprotein
HDM(s): Histone demethylase(s)
hmdC: 5-hyd0072oxymethyl-2′-deoxycytidine
HNF4α: Hepatocyte nuclear factor 4 α also known as nuclear receptor subfamily 2, group A, member 1
HMT(s): Histone methyltransferase(s)
HNF4α: Hepatocyte nuclear factor 4α
HRV: Heart-rate-variability
hTERT: Gene encoding human telomerase reverse transcriptase a catalytic subunit of the enzymetelomerase
IEE: Increased energy expenditure
IGF1: Insulin-like growth factor 1 also known as somatomedin C
IL-1β: Human interleukin 1β
c-KIT: Proto-oncogene c-Kit also known as mast/stem cell growth factor receptor, also known as tyrosine-protein kinase Kit or CD117
IRS: Insulin receptor substrate
KEAP-1: Kelch-like ECH-associated protein 1
Ku70: Protein encoded in humans by the gene *XRCC*6
LBK1: Tumor suppressor kinase enzyme that activates AMPK
LDL: Low-density lipoprotein
miRNA(s): microRNA(s)
mRNA: Messenger RNA
mSin1: Mammalian stress-activated protein kinase-interacting protein
MTH: Mitochondrion, mitochondrial
mTOR: Mammalian target of rapamycin
mTORC1: Mammalian target of rapamycin complex 1
mTORC2: Mammalian target of rapamycin complex 2
NAD^+: Nicotinamide adenine dinucleotide
NADH: NADH dehydrogenase
NF-κB: nuclear factor kappa B
NIP7: 60S ribosome subunit biogenesis protein NIP7 homolog
NMDA: N-Methyl-D-aspartic acid or N-Methyl-D-aspartate

$p16^{INK4a}$: Gene encoding the tumor suppressor protein cyclin-dependent kinase inhibitor 2A or CDKN2A or multiple tumor suppressor 1 (MTS-1)
PDPK1: 3-phosphoinositide-dependent protein kinase-1
PGC1-α: Peroxisome proliferator-activated receptor G co-activator 1α
p53: Tumor suppressor protein p53 also known as tumor protein 53
p47phox: Subunit of NADPH oxidase, that has to be phosphorilated for the activation of NADPH oxidase
PKA: Protein kinase A
PKC: Protein kinase C
PKG: Protein kinase G, or cGMP-dependent protein kinase
PtdIns-3K: Phosphatidylinositol 3-kinase
RAP: Rapamycin
RAPTOR: Regulatory-associated protein of mTOR
RHEB: RAS homolog enriched in brain protein, binds GTP
RNA: Ribonucleic acid
ROS: Reactive oxygen species
RSV: Resveratrol
RAS: Protein superfamily of small GTPases
RTG1: Retrograde regulation protein 1
RUNX3: Gene encoding runt-related transcription factor 3
S6 K1: Ribosomal protein S6 kinase β-1
SGK1: Serum-and glucocorticoid-regulated kinase; a serine/threonine protein kinase
SIRT1: NAD-dependent-deacetylase sirtuin1 also known as silent mating type information regulation 2 homolog 1
SOCS-3: Suppressor of cytokine signaling 3
sTNRF1: Soluble tumor necrosis factor receptor 1
TLR-4: Toll-like receptor 4
TNFα: Tumor necrosis factor α
TOR: Target of rapamycin
TSC1: Tuberous sclerosis protein 1 also known as hamartin
TSC2: Tuberous sclerosis protein 2 also known as tuberin
VDAC1: Voltage-dependent anion-selective channel protein 1
TIG1: Tazarotene-induced gene-1
WT1: Gene encoding Wilms tumor protein
YY1: Transcriptional repressor protein YY1.

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