Cell

Leading Edge
Review

Metabolic Control of Longevity

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http://dx.doi.org/10.1016/j.cell.2016.07.031

Several metabolic alterations accumulate over time along with a reduction in biological fitness, suggesting the existence of a "metabolic clock" that controls aging. Multiple inborn defects in metabolic circuitries accelerate aging, whereas genetic loci linked to exceptional longevity influence metabolism. Each of the nine hallmarks of aging is connected to undesirable metabolic alterations. The main features of the "westernized" lifestyle, including hypercaloric nutrition and sedentariness, can accelerate aging as they have detrimental metabolic consequences. Conversely, lifespan-extending maneuvers including caloric restriction impose beneficial pleiotropic effects on metabolism. The introduction of strategies that promote metabolic fitness may extend healthspan in humans.

Introduction

The human superorganism (i.e., the host and its microbiome) is a complex metabolic system in which nutrient intake, physical activity, and elimination of waste orchestrate anabolic and catabolic reactions that ultimately determine development, maturation, and aging. After many years of being subordinate to the surge in cellular and molecular biology, the study of metabolism is now experiencing its own Renaissance. A clear understanding is emerging of the key roles that metabolites play in all biological processes, including physiological and pathological aging.

Recent trans-species comparisons have tried to link longevity with metabolic parameters from different organs (Ma et al., 2015a). These studies have revealed a positive correlation between longevity and sphingomyelin levels. Conversely, the levels of triacylglycerols containing polyunsaturated fatty acid (PUFA) side chains and by-products of inflammatory processes correlate negatively with longevity. Consistently, female familial longevity in humans has been associated with high levels of plasma sphingomyelin and low levels of PUFA-containing triacylglycerols (Gonzalez-Covarrubias et al., 2013). Longevity across mammalian species also correlates negatively with the hepatic levels of enzymatic cofactors involved in amino acid metabolism and with the hepatic concentrations of tryptophan degradation products. Accordingly, reduction of dietary amino acids—notably, tryptophan and methionine—can extend lifespan in animal models (Fontana and Partridge, 2015). Hence, a reduced energy expenditure per body mass per day (mass-specific basal metabolism) may characterize long-lived mammals.

Multiple studies have tried to determine the biological age of humans by measuring proxies including telomere length, gene methylation (that would reflect an "epigenetic clock"), and transcriptional signatures (that would mirror "transcriptomic aging") (Peters et al., 2015). Similarly, it has been attempted to determine aging-related metabolic features. Thus, NMR spectroscopy has been used to measure age-associated changes in the urine metabolome and to determine a "metabolic age score," which was shown to predict survival independent of chronological age and other risk factors (Hertel et al., 2016). Consistently, age-associated alterations and some premature manifestations of age-related diseases in humans can be detected in the serum metabolome and lipidome (Gonzalez-Covarrubias et al., 2013).

Moreover, two of the nine hallmarks of aging that we have previously defined, namely, "deregulated nutrient sensing" and "mitochondrial dysfunction," are tightly linked to metabolic alterations. Similarly, the hallmark "altered intercellular communication," which gathers any age-related change that trespasses the boundaries of single cells, encompasses major biochemical and neuroendocrine alterations affecting whole-body metabolism (López-Otín et al., 2013). In line with this consideration, many human gene variants that increase the likelihood of becoming a centenarian—such as those in forkhead box O3 (*FOXO3*) and other genes involved in PI3K/AKT1 signaling—are linked to metabolism (Broer and van Duijn, 2015). Moreover, the male offspring of two parents reaching a nonagenarian age exhibits reduced abdominal visceral fat, suggesting that familial longevity is linked to a healthy metabolic profile (Sala et al.,

2015). Conversely, many genetic syndromes that cause premature aging in humans are directly linked to metabolic defects. This applies to cutis laxa (defects in proline biosynthesis), Ehlers-Danlos syndrome (deficient proteoglycan synthesis), the Lenz-Majewski hyperostotic dwarfism (defects in phosphatidylserine synthesis), SHORT syndrome (hypomorphic mutations in *PIK3R1*), and progressive external ophtalmoplegia (mitochondrial DNA instability) (Vermeij et al., 2016). Although most other genetically determined progeroid syndromes stem from alterations in genes that maintain genome integrity, and hence affect metabolism indirectly, these examples underscore a potential key role for metabolic deficiencies in aging.

Here, we describe the links between each hallmark of aging and metabolic perturbations, discuss current strategies to manipulate metabolism for increasing healthspan and lifespan, and elaborate on the major threat posed to public health in the developed world, i.e., the incipient ''westernization'' of lifestyle.

Metabolic Repercussions of the Hallmarks of Aging

We have previously classified the nine candidate hallmarks of aging into three categories (López-Otín et al., 2013). The primary hallmarks (genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis) are the main causes of molecular damage underlying aging. The antagonistic hallmarks (deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence) mediate beneficial effects at low levels and protect the organism from damage and nutrient scarcity but become deleterious at high levels. Finally, the integrative hallmarks (stem cell exhaustion and altered intercellular communication) are the culprits of aging and arise when the accumulating damage cannot be compensated by homeostatic mechanisms. All these denominators of aging have important repercussions on cellular metabolism (Figure 1).

Genomic Instability

Nuclear DNA damage and the consequent activation of repair mechanisms have multiple effects on cellular metabolism. Patients with age-accelerating diseases such as Hutchinson-Gilford progeria syndrome and Werner syndrome frequently develop type 2 diabetes, suggesting that chronic DNA damage can promote metabolic disorders (Shimizu et al., 2014). Mouse models with defective transcription-coupled repair (for instance upon knockout of *Ercc1*) exhibit multiple biochemical aberrations including altered nutrient sensing, energy metabolism, and redox balance. This complex response to persistent DNA damage not only affects all circuitries underlying bioenergetic metabolism (mitochondrial oxidative phosphorylation, glycolysis, and the pentose phosphate shunt required for antioxidant defense) but also blocks the anabolic reactions driven by trophic signals such as insulin (INS), insulin-like growth factor 1 (IGF1), and growth hormone 1 (GH1), which are required for cell growth and proliferation (Garinis et al., 2008). This situation may reflect a strategy whereby cells experiencing DNA damage and other forms of stress favor adaptive processes over anabolic reactions. Indeed, several components of the DNA-repair machinery, including Chek1 and p53, are phosphorylated and inhibited by the growth factor-responsive kinase Akt1 (Vermeij et al., 2016).

The systemic or tissue-specific knockout of *Ercc1* is sufficient to cause the dissociation of a multiprotein complex containing nuclear receptor corepressor 1 (Ncor1), Ncor2, and histone deacetylase 3 (Hdac3) from the promoters of interleukin 6 (Il-6), Il-8, and tumor necrosis factor (Tnf) in mouse adipocytes. The consequent secretion of pro-inflammatory cytokines promotes chronic inflammation and lipodystrophy. Importantly, the adipocyte-specific knockout of one *Ercc1* allele causes type 2 diabetes, confirming that DNA-damage responses in selected cell types can provoke a systemic perturbation of metabolism (Karakasilioti et al., 2013). Cells experiencing DNA damage also secrete type I interferon, which amplifies the response to damage, induces cellular senescence, and inhibits stem cell function. Consistently, suppression of type I interferon signaling abrogates the establishment of various progeroid phenotypes in mice with erosion-prone telomeres (Yu et al., 2015).

Some of the best-studied human progerias, ataxia telangiectasia, Cockayne syndrome, and xeroderma pigmentosum, are disorders of nucleotide excision repair characterized by severe neurodegeneration. These diseases are accompanied by the hyperactivation of poly(ADP-ribose) polymerase 1 (PARP1), a nicotinamide adenine dinucleotide (NAD^+)-dependent enzyme involved in DNA repair. PARP1 hyperactivation leads to NAD^+ depletion, hence inhibiting the NAD^+-dependent deacetylase sirtuin 1 (SIRT1) (Fang et al., 2014). These events lead to mitochondrial abnormalities, including reactive oxygen species (ROS) generation, increased transmembrane potential, and limited mitochondrion-selective autophagy (mitophagy), all of which can be rescued in mice by PARP1 inhibition or external supply of the NAD^+ precursor nicotinamide riboside (Fang et al., 2014; Scheibye-Knudsen et al., 2014). Mechanistically, these effects (which result in the accumulation of dysfunctional mitochondria) stem from reduced peroxisome proliferator-activated receptor gamma (PPARG) coactivator 1 alpha (PPARGC1A; best known as PGC1α) activity and consequent uncoupling protein 2 (UCP2) downregulation (Fang et al., 2014). Thus, genomic instability may trigger different metabolic alterations that favor cellular senescence and organismal aging.

Telomere Attrition

Telomere shortening caused by telomerase inactivation can precipitate aging in mice. However, telomerase also has telomere-independent functions that counteract premature aging, a finding that should stimulate further assessments of the relative role of telomerase and telomere erosion in the aging process. Telomere attrition ensuing the knockout of telomerase reverse transcriptase (*Tert*) or telomerase RNA component (*Terc*) accelerates aging as it causes insulin resistance, β cell failure, and glucose intolerance (Shimizu et al., 2014). Telomere attrition also promotes p53 activation, hence causing the repression of Pgc1α and Pgc1β, the consequent suppression of the transcription factors nuclear respiratory factor 1 (Nrf1), estrogen-related receptor alpha (Esrra), and Ppara, and hence the inhibition of mitochondrial biogenesis and function (Sahin et al., 2011). Thus, telomere erosion may limit mitochondrial turnover and favor age-related metabolic perturbations, at least in mice. Telomere dysfunction also enhances the requirement of glucose for the maintenance of energy homeostasis, as well as for mechanistic target of rapamycin (Mtor)- and Igf1-dependent mitochondrial biogenesis, in mouse aging tissues. Accordingly, a glucose-enriched diet significantly extends the lifespan of $Terc^{-/-}$ mice

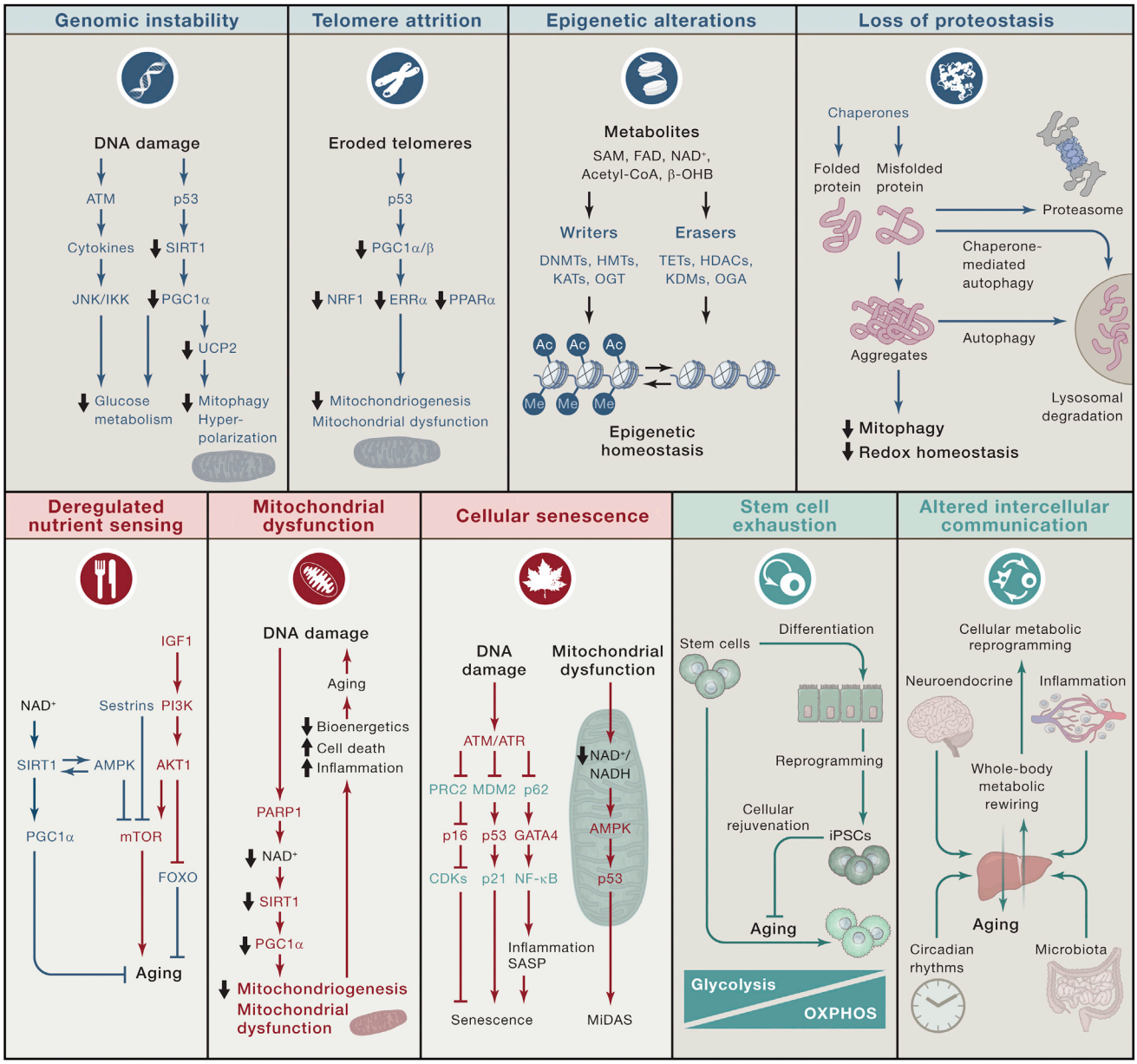

Figure 1. Metabolic Impact of the Hallmarks of Aging
All hallmarks of aging, including primary hallmarks (blue background), antagonistic hallmarks (red background), and integrative hallmarks (green background) have prominent repercussions on anabolic or catabolic metabolism.

by stimulating glycolysis, mitochondrial biogenesis, and oxidative glucose metabolism (Missios et al., 2014).

Several metabolic alterations linked to telomere attrition are detectable in humans. In a cohort of 3,511 women, leukocyte telomere length (LTL) negatively correlated with two markers of oxidative stress, γ-glutamyltyrosine and γ-glutamylphenylalanine, as well as with two lysolipids that are positively associated with phospholipase A2 expression and may reflect poor membrane fluidity (Zierer et al., 2016). These results, which have been confirmed in an independent cohort of 904 women, suggest that telomere length might influence metabolism (or vice versa) in humans. The existence of such a cause-effect relationship remains to be explored in suitable animal models. Of note, dietary interventions performed in humans suggest that a Mediterranean diet with a strong "anti-inflammatory" profile may slow LTL shortening (García-Calzón et al., 2015), although these findings are mostly correlative. Beyond these pending questions, current evidence indicates that telomere attrition triggers metabolic changes that also impinge on other hallmarks of aging, including mitochondrial dysfunction, stem cell exhaustion, and altered intercellular communication.

Epigenetic Alterations

Aging is accompanied by multiple epigenetic alterations, and many of the enzymes that catalyze these changes utilize cofactors and substrates generated by intermediate metabolism, suggesting the existence of a strong link between the epigenetic control of aging and metabolism (Benayoun et al., 2015). Accordingly, the enhancer and insulator regions of genes whose expression levels in peripheral blood change with age tend to be enriched in functional CpG methylation sites. Moreover, the premature upregulation of the so-called "transcriptomic age" (an age-associated metagene) of an individual has been associated with signs of metabolic syndrome, such as enhanced blood pressure, increased levels of circulating glucose and cholesterol, as well as high body-mass index (Peters et al., 2015). Indeed, accumulating data indicate that major metabolic shifts, such as starvation-induced reduction of acetyl-coenzyme A and methionine restriction-associated depletion of S-adenosylmethionine (SAM), affect chromatin acetylation and methylation, respectively, leaving a durable epigenetic signature of past metabolic experiences that may condition the organismal response to future challenges (Su et al., 2016). Such epigenetic mechanisms, as well as alterations in small non-coding RNA levels, may also explain how parental obesity or other metabolic alterations experienced during gestation and lactation may favor the transmission of various aspects of metabolic syndrome to the next generation.

Irrespective of the underlying mechanisms, the "transmission" of metabolic signatures from one generation to the next may be difficult to explain by a simple pattern of epigenetic alterations affecting all cell types. For instance, feeding mouse dams a high-fat diet during lactation strongly inhibits the formation of projections of anorexigenic proopiomelanocortin (POMC)- and orexigenic agouti-related neuropeptide (AGRP)-producing neurons in the hypothalami of newborns, most likely as a result of hyperinsulinemia, which altogether predisposes the offspring to hyperphagia, obesity, and diabetes (Vogt et al., 2014). Interestingly, such a protocol of transgenerational metabolic derangement decreases the expression levels of DNA methyltransferase 1 (Dnmt1) in the hypothalamus of the newborn and also affects the levels of Sirt1 and Hdac1 (another histone deacetylase) into adulthood (Desai et al., 2016). Altogether, these findings suggest that epigenetic traits are profoundly affected by past metabolic experiences, both within an individual's aging trajectory and across generations. It is therefore likely that manipulating the epigenome by metabolic interventions or by enhancing the activity of relevant enzymes, such as SIRT6, may improve various manifestations of age-related diseases and extend healthspan.

Loss of Proteostasis

Aging and various aging-associated diseases are associated with impaired proteostasis (protein homeostasis) (Labbadia and Morimoto, 2015). The integrity of the proteome is preserved by folding mechanisms involving a complex network of molecular chaperones, as well as by degradation processes mediated by the ubiquitin-proteasome and the autophagy-lysosome systems. Signaling pathways that impinge on intermediate metabolism and regulate proteostasis influence aging as well as the onset and progression of age-related diseases (Vilchez et al., 2014). For example, metabolites from the hexosamine pathway enhance protein quality control, improve resistance to proteotoxic stress, and increase lifespan in animal models (Denzel et al., 2014). Conversely, proteotoxic stress associated with aging causes the loss of redox homeostasis, triggering adaptive changes in multiple subcellular compartments. Moreover, age-related metabolic and bioenergetic changes reduce the activity and availability of ATP-dependent chaperones, further hampering the preservation of cellular and organismal proteostasis (Brehme et al., 2014).

Proteasome activity also declines with time, a process that markedly alters the proteome of aging cells and tissues. In contrast, healthy centenarians maintain remarkable proteasomal activity (Chondrogianni et al., 2015). The age-related decline in proteasomal efficiency may have detrimental metabolic outcomes. Indeed, the beneficial effect of elevated proteasomal activity on yeast lifespan has been attributed to its impact on AMP-activated protein kinase (AMPK) signaling (Yao et al., 2015). Robust proteasomal functions also correlate with an elevated respiratory activity and increased oxidative stress response. Consistently, genomic studies have revealed that polymorphisms affecting different proteasomal subunits are associated with increased susceptibility to metabolic disorders including diabetes in humans.

Moreover, one of the most important alterations that accompanies normal aging is a decline in autophagic proficiency (Madeo et al., 2015). Although most work on this topic has focused on macroautophagy, defects in chaperone-mediated autophagy (CMA) have also been documented in the aging mouse liver. Thus, the liver-specific knockout of lysosomal-associated membrane protein 2 (*Lamp2*) induces the accumulation of key enzymes of carbohydrate and lipid metabolism in hepatocytes, which is paralleled by a reduction in gluconeogenesis, an increase in glycolysis, and hepatic steatosis (Schneider et al., 2014). Reduced mitophagy has also been associated with aging, at least in specific brain areas (Sun et al., 2015).

Genetic manipulations designed to promote autophagy, such as systemic overexpression of the essential component of the autophagic machinery Atg5, increase longevity and improve insulin sensitivity, leanness, and motor function in mice (Pyo et al., 2013). Similarly, transgene-driven expression of transcription factor EB (*TFEB*; a pro-autophagic transcriptional regulator) increases lifespan in *Caenorhabditis elegans* and antagonizes the lipotoxicity of high-fat diet in mice (Settembre et al., 2013). Accumulating evidence suggests that any kind of manipulation that extends lifespan loses its beneficial effect when autophagy is inhibited (Madeo et al., 2015). Importantly, deficient autophagy also plays an unexpected key role in animal models of accelerated aging, such as mice deficient in klotho (*Kl*), which develop a progeria-like syndrome accompanied by arteriosclerosis and reduced levels of autophagy at baseline (Kurosu et al., 2005; Shi et al., 2015). Conversely, transgene-driven *Kl* overexpression extends lifespan (Kurosu et al., 2005), and recombinant Kl injection into mice promotes cytoprotective autophagy (Shi et al., 2015). These results suggest that differences in Kl expression might affect the aging process secondary to alterations in autophagic flux.

Paradoxically, mice lacking zinc metallopeptidase STE24 (*Zmpste24*)—which are a model of Hutchinson-Gilford progeria syndrome—exhibit increased autophagic flux associated with

metabolic changes that normally accompany lifespan extension (Mariño et al., 2008). These metabolic alterations are linked to changes in circulating leptin, glucose, insulin, and adiponectin levels, which altogether lead to peripheral AMPK activation and MTOR inhibition. It has therefore been proposed that the nuclear damage causing premature aging in *Zmpste24*$^{-/-}$ mice triggers a metabolic response involving the compensatory activation of autophagy. However, the chronic activation of this pathway turns a pro-survival mechanism into an etiological determinant of the systemic degeneration found in *Zmpste24*$^{-/-}$ progeroid mice (Mariño et al., 2008).

In summary, metabolic changes associated with aging can impinge on the collapse of the proteostasis network and vice versa. Recent findings suggesting that the integrity of the cellular proteome is also preserved systemically, via non-cell-autonomous mechanisms, emphasize the need to identify the metabolic factors that may extend longevity by preventing age-associated proteome degeneration.

Deregulated Nutrient Sensing

Different signaling pathways that sense and respond to fluctuations in nutrient levels are commonly deregulated during aging and in the presence of metabolic disorders (Efeyan et al., 2015). Among them, the ''insulin and IGF1 signaling'' (IIS) pathway has prominent aging-modulating effects. Consistent evidence indicates that the most efficient measure to extend lifespan across species, namely, caloric restriction (CR), relies on the suppression of the IIS pathway, coupled to the activation of various members of the FOXO protein family, and MTOR inhibition. Accordingly, nematodes overexpressing the FOXO-like transcription factor DAF-16 or lacking the worm ortholog of MTOR (i.e., LET-363) exhibit considerable lifespan extension as compared to control worms (Lapierre and Hansen, 2012). Paradoxically, normal aging as well as the aging-accelerating effects of obesity (see below) can be linked to the progressive inactivation of the IIS pathway, perhaps as a response aimed at minimizing cell growth in the context of systemic damage (Garinis et al., 2008).

Other nutrient sensors, in particular AMPK and sirtuins, tend to be downregulated with aging, and their pharmacological activation is reputed to increase longevity. In *C. elegans*, the α subunit of AMPK (i.e., AAK-2) is required for the lifespan-extending effects of several genetic interventions, and AAK-2 overexpression per se increases lifespan (Lapierre and Hansen, 2012). Among age-regulating sirtuins, SIRT1 is shut off secondary to the age-associated depletion of its main cofactor, NAD^+. The mechanisms accounting for NAD^+ loss are presumably multifactorial, encompassing downregulation of the biosynthetic enzyme nicotinamide phosphoribosyltransferase (NAMPT), hyperactivation of the NAD^+-consuming enzyme PARP1, disruption of circadian rhythms, and chronic inflammation (Verdin, 2015). Sestrins—a family of stress-inducible proteins that modulate nutrient-sensing pathways such as those orchestrated by AMPK and MTOR—are also emerging as regulators of metabolic homeostasis and appear to attenuate aging in various model organisms (Lee et al., 2013). The lack of sestrin 3 (*Sesn3*) in mice results in diverse metabolic disorders that generally accompany accelerated aging, including fat accumulation, diabetes, and muscle degeneration. Conversely, transgenic *Sesn3* expression protects mice against insulin resistance caused by high-fat diet, as a direct consequence of MTOR complex 2 (MTORC2)-Akt1 signaling (Tao et al., 2015). Interestingly, Sesn2 is a leucine sensor for the MTORC1 pathway, connecting the availability of this amino acid to the control of organismal growth (Wolfson et al., 2016). Thus, proficient nutrient-sensing pathways are required to preserve metabolic fitness at the organismal level and hence suppress the development of aging-associated diseases.

Mitochondrial Dysfunction

Human aging is generally linked to a progressive mitochondrial dysfunction (Wang and Hekimi, 2015). Part of this deterioration is caused by the abovementioned decrease in NAD^+ availability and consequent functional impairment of the deacetylase SIRT1 (Gomes et al., 2013). Indeed, low SIRT1 activity results in the acetylation-dependent inactivation of PGC1α, MYC, and HIF1A, which limits the PGC1α-dependent expression of nuclear genes encoding mitochondrial proteins, as well as the MYC- and HIF1A-dependent expression of the mitochondrial transcription factor TFAM (Gomes et al., 2013). This example illustrates how alterations in the intracellular levels of one single metabolite can contribute to mitochondrial aging by impairing mitonuclear communication.

Paradoxically, mild perturbations of mitochondrial function can extend longevity in various model organisms (Palikaras et al., 2015). The mechanisms accounting for this counterintuitive finding have been elucidated in *C. elegans*, where partial mitochondrial dysfunction extends longevity upon epigenetic changes linked to histone demethylation (Merkwirth et al., 2016) and coupled to the activation of multiple transcription factors including the worm orthologs of mammalian p53, NRF2, and HIF1A (Ventura et al., 2009). Upon stabilization, HIF1A activates the xenobiotic detoxification enzyme flavin-containing monooxygenase-2 (FMO-2), which contributes to promoting longevity in worms (Leiser et al., 2015). Moreover, mitophagy induction by the worm ortholog of NRF2 (SKN-1) is required for the longevity-extending effects of mild mitochondrial dysfunction (Palikaras et al., 2015). Intriguingly, adaptive responses to mild mitochondrial perturbations can activate a longevity-promoting mechanism that depends on proteins usually involved in cell death signaling (Yee et al., 2014).

Mouse mitochondria can release peptides such as humanin and MOTS-c (encoded within *mt-Rnr2* and *mt-Rnr1*, respectively) with potential longevity-extending activity. Humanin has cytoprotective effects in vitro and ameliorates cardiovascular and neurodegenerative disorders in rodents (Yen et al., 2013). MOTS-c promotes the biosynthesis of an endogenous AMP analog, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), which stimulates AMPK and hence counteracts diabetes, obesity, and aging (Lee et al., 2015). Intriguingly, a polymorphism in the MOTS-c-coding sequence of *mt-Rnr1* is frequent among Northeast Asians, and this may partially contribute to the exceptional longevity of the Japanese population (Fuku et al., 2015).

The predominant link between mitochondria and longevity may consist in the acceleration of mitochondrial turnover, implying a combination of increased synthesis (Finley et al., 2012) and mitophagic degradation (Palikaras et al., 2015), globally assuring optimal quality control. Preserving mitochondrial

fitness is expected to have a beneficial impact on several aspects of the aging process, including not only primary mitochondrial function but also (1) genomic instability (dysfunctional mitochondria are major sources of genotoxic ROS; see above) and (2) altered intercellular communication (ROS overgeneration is connected to the secretion of inflammatory mediators, see below). Further substantiating this notion, both PGC1α levels and mitophagy decline with age in mice (Chabi et al., 2008). It has been speculated that the mitochondrial unfolded protein response (UPR^{mt})—an adaptive reaction initiated by the accumulation of aberrant proteins in the mitochondrial matrix or by an unbalanced mitonuclear communication—may underlie the ability of mild perturbations of mitochondrial homeostasis to extend longevity in *C. elegans* (Wang and Hekimi, 2015). Recently, the lifespan-extending effects of nicotinamide riboside have been linked to the activation of the UPR^{mt} in various stem cell compartments in mice (Zhang et al., 2016), suggesting that the UPR^{mt} may be important for longevity in several organisms beyond worms.

Cellular Senescence

Accumulating in vitro and in vivo evidence indicates that cellular senescence —a process that imposes a permanent proliferative arrest on cells responding to different stressors—is intimately associated with several metabolic alterations. The available data linking cellular senescence with aging and aging-associated diseases, including metabolic disorders, are mainly circumstantial. However, targeted clearance of senescent cells from progeroid mice reduces circulating levels of activin A, enhances adipogenesis, and prevents lipodystrophy, a common feature of advanced age (Xu et al., 2015). Furthermore, the elimination of naturally occurring senescent cells has recently been shown to attenuate the age-related deterioration of several organs and tissues and to extend lifespan in mice (Baker et al., 2016).

The so-called "senescence-associated secretory phenotype" (SASP), which is a pathognomonic shift in protein secretion, stems from the dissociation of the transcription factor GATA4 and the autophagic adaptor p62 (Kang et al., 2015). Such dissociation abolishes the autophagic degradation of GATA4 and hence allows it to support the SASP and consequent inflammatory response, which is a driver of aging. This mechanism links cellular senescence to another hallmark of aging, altered intercellular communication, via a metabolic effect on autophagy. Autophagy may also contribute to senescence triggered by DNA damage through a specific mechanism in which a nuclear pool of LC3 (a core component of the autophagic machinery) interacts with lamin B1 and damaged heterochromatin, hence favoring their export to the cytoplasm and lysosomal degradation (Dou et al., 2015). Autophagy inhibition limits oncogene-induced senescence in human cells, but nutrient deprivation (which potently activates autophagy) per se does not cause the degradation of lamin B1 and senescence (Dou et al., 2015). This may be linked to the subcellular localization of LC3, which is mostly nuclear in fed cells but upon starvation shuttles to the cytoplasm, where it is deacetylated by SIRT1 and interacts with other components of the autophagic machinery.

Interestingly, mitochondrial dysfunction can precipitate a peculiar type of cellular senescence that has been dubbed "mitochondrial dysfunction-associated senescence" (MiDAS). At odds with other forms of cellular senescence, MiDAS does not involve IL-1β secretion but promotes the release of other conventional components of the SASP, including IL-10, TNF, CCL27, and HMGB1 (Wiley et al., 2016). MiDAS is characterized by reduced NAD^+/NADH ratio, which causes growth arrest and prevents IL-1β secretion as a result of AMPK-driven p53 activation. Although MiDAS appears to be rather frequent in homozygous $Polg^{D257A/D257A}$ mice, which have a progeroid phenotype linked to an increased rate of mitochondrial DNA mutations (Wiley et al., 2016), the exact contribution of this phenomenon to the aging process remains to be determined. Nonetheless, MiDAS provides additional support to the existence of strong connections between cellular senescence and metabolic dysfunction. Furthermore, the fact that some senolytic agents (i.e., compounds that selectively remove senescent cells from tissues) and SASP inhibitors target central metabolic pathways, alleviate adipose tissue dysfunction, and improve metabolism in aged mice suggests that targeting metabolism may be part of future approaches aimed at extending lifespan in humans.

Stem Cell Exhaustion

The progressive decline in stem cell function that generally accompanies aging may result from many of the aforementioned hallmarks of aging, alone or in combination, and hence is intimately linked to metabolic alterations. Heterochronic transplantation experiments (in which tissues from an aged mouse are transplanted into a young mouse or vice versa) and parabiosis studies (in which the circulatory system of an aged mouse is shared with a young mouse) have delineated some of the metabolic alterations that affect stem cell aging (Goodell and Rando, 2015). Metabolic assessments have also revealed that, as they age, stem cells experience important changes in the balance between glycolysis, oxidative phosphorylation, and response to oxidative stress (Shyh-Chang et al., 2013). Stem cells in general, including hematopoietic stem cells (HSCs), are particularly sensitive to ROS, and ROS increase with age in this cellular compartment. Accordingly, treatment with the antioxidant *N*-acetyl-*L*-cysteine enhances the replicative potential of mouse HSCs in serial transplantation experiments (Ito et al., 2006). Nutrient sensors including the insulin receptor (INSR), MTORC1, and AMPK, as well as downstream signal transducers like PI3K, AKT1, and FOXO transcription factors, also modulate the balance between stem cell quiescence and proliferation in the course of aging, at least in mice. For example, excessive MTOR signaling causes epidermal stem cell exhaustion and hair loss (Castilho et al., 2009), defects in the FOXO system dampen the oxidative stress response and promote HSC depletion, and alterations in AMPK signaling contract the size of long-term HSC pools and impair hematopoiesis (Shyh-Chang et al., 2013). Of note, SIRT7 is downregulated in HSCs from old individuals, which causes unwarranted NRF1-dependent mitochondrial biogenesis, incapability to maintain the quiescent state, and myeloid-biased differentiation (Mohrin et al., 2015). Thus, a reduced number of mitochondria paradoxically appears to be an inalienable property of stem cells.

Intermediate metabolites from glycolytic and oxidative reactions also influence epigenetic changes that accompany the reprogramming of differentiated cells into induced pluripotent stem cells (iPSCs) (Ryall et al., 2015). iPSCs rely on glycolysis

to generate ATP and have reduced mitochondrial mass as compared to somatic cells. The inhibition of autophagy-related proteins like Ulk1 and Rab9, as well as that of their upstream activator AMPK, can prevent the wave of mitochondrial clearance that accompanies the reprogramming of somatic cells into iPSCs, whereas multiple autophagy inducers favor the iPSC generation (Ma et al., 2015b). These findings suggest that non-canonical autophagy may contribute to the generation of iPSCs. It has not been determined yet whether this atypical autophagic pathway crosstalks with NF-κB signaling, which has a major inhibitory effect on iPSC generation as it activates the repressor DOT1L (Soria-Valles et al., 2015). Further studies of the impact of metabolism on the age-related exhaustion of stem cells, as well as on the metabolic aspects of stem cell reprogramming, will likely result in new approaches for modulating aging at the cellular level or even prolonging organismal longevity.

Altered Intercellular Communication

Multiple age-related alterations of metabolism are intertwined with major perturbations in intercellular communication. Such an intersection between metabolism and the orchestration of multicellular life concerns a variety of complex processes including neuroendocrine signaling, inflammation, and circadian rhythms. Even the gut microbiota of the elderly differs from that of the young, in particular as it contains a reduced abundance of *Ruminococcus spp.* and *Prevotella spp.*, correlating with signs of frailty, co-morbidity, and inflammation (Claesson et al., 2012). Experiments in young mice demonstrate that depleting the gut microbiota favors browning of white adipose tissue and reduces obesity (Suárez-Zamorano et al., 2015), and aging is well-known to involve a re-organization of whole-body metabolism that causes a reduction in brown and beige fat. However, the actual relationship between age-associated changes in the gut microbiota and brown fat reduction has not been investigated thus far. Neuroendocrine circuits affecting metabolic phenotypes also change over time, and some of them constitute targets for the experimental extension of longevity. As an example, the knockout of *Trpv1*, which encodes a specific pain receptor, improves metabolic fitness and extends survival in mice by limiting the production of the neuropeptide Cgrp from sensory terminals innervating pancreatic islets (Riera et al., 2014). This situation favors insulin secretion, which would otherwise decline with age due to the enhanced local secretion of Cgrp.

Age-associated inflammation and consequent insulin resistance, bone loss, cognitive decline, and frailty can be reduced by genetic ablation of the NLRP3 inflammasome, a multicomponent platform responsible for the secretion of mature IL-1β and IL-18 (Goldberg and Dixit, 2015). In the course of aging, NLRP3 (which normally responds to microbial or neoplastic threats) is activated by the accumulation of endogenous danger signals including ATP, cholesterol crystals, excess glucose, and urate in the extracellular space, a process that is further favored by intracellular ROS overgeneration secondary to mitochondrial dysfunction. Interestingly, ketone bodies that rise upon fasting (i.e., β-hydroxybutyrate) potently inhibit the NLRP3 inflammasome (Youm et al., 2015), proving another link between CR and lifespan extension. In the visceral adipose tissue (VAT), fat-resident regulatory T (fT_{reg}) cells accumulate with age. Depletion of fT_{reg} cells by conditional knockout of *Pparg* abolishes virtually all age-related metabolic changes, as it ameliorates insulin sensitivity and glucose uptake by VAT (Bapat et al., 2015). Such improvements can be partially recapitulated by acute fT_{reg} depletion with an antibody that neutralizes the IL-33 receptor interleukin-1 receptor-like 1 (Il1rl1, also known as St2) and are specific for age-associated insulin resistance, but not for obesity-driven metabolic syndrome. Conversely, both aging and obesity are associated with an exacerbated secretion of transforming growth factor beta 1 (TGF-β1) by hypothalamic astrocytes, constituting a common determinant of glucose intolerance and insulin resistance (Yan et al., 2014). Thus, obesity and aging cause insulin resistance through inflammatory pathways that overlap only to partial extents.

Aging correlates with a decrease in the circadian oscillation of the so-called "respiratory exchange ratio" (which reflects the relative consumption of carbohydrate or lipid for energy metabolism), and old mice develop a substrate preference toward lipids, losing the capacity to switch between distinct fuel sources, which is commonly referred to as "metabolic flexibility." Although this phenotype might stem from declining mitochondrial proficiency and the development of insulin resistance, it may also be associated with changes in circadian control. Aging has been linked to an attenuated circadian oscillation in transcriptional processes of the suprachiasmatic nucleus of the hypothalamus (and perhaps of other cell-autonomous clocks in the periphery as well), which in turn has been attributed to declining NAD^+ levels (Chang and Guarente, 2013). Such a decline reflects a decrease in NAMPT expression levels and inhibits SIRT1 deacetylase activity. SIRT1 contributes to the regulation of circadian rhythms by a transcriptional mechanism impinging on the deacetylation of histone H3, aryl hydrocarbon receptor nuclear translocator-like (Arntl, also known as Bmal1), and period circadian clock 2 (Per2) (Asher et al., 2008). In addition, SIRT1 deacetylates acyl-CoA synthetase long-chain family member 1 (Acsl1), thereby causing circadian oscillations of acetyl-CoA levels (Sahar et al., 2014), with wide-ranging consequences for several metabolic circuitries, including autophagy. The complex crosstalk between circadian clocks and metabolic pathways through mechanisms that decay with aging also involves polyamines (e.g., putrescine and spermidine). Indeed, the availability of polyamines oscillates with circadian periodicity, mostly reflecting feeding behavior (Zwighaft et al., 2015). Reciprocally, putrescine and spermidine control the circadian period in cultured cells and mice by modulating the interaction between the core clock proteins Per2 and cryptochrome 1 (Cry1). In mice, the age-related decline in polyamine levels is linked to an increased circadian periodicity, which can be reversed upon dietary polyamine supplementation (Zwighaft et al., 2015). Collectively, these studies offer novel targets for metabolic and nutritional interventions aimed at preventing the functional decay of the circadian clock over time.

Metabolic Interventions to Improve Longevity

Several metabolic interventions can increase longevity, including global CR, the selective limitation of specific nutrients like methionine, physical exercise, and the administration of agents—which we refer to as "CR mimetics" (CRM)—that mimic the

Table 1. Metabolic Interventions to Extend Healthspan or Lifespan in Mice

Intervention	Observations	References
Acarbose (α-glycosidase inhibitor)	decreases serum IGF1 levels and increases FGF21; exhibits superior lifespan-extending activity in male mice.	Harrison et al., 2014
Branched amino acid mix (valine, leucine, isoleucine)	increases lifespan coupled to increased SIRT1 expression and mitochondrial biogenesis.	D'Antona et al., 2010
Butyrate supplementation	extends lifespan *in Zmpste24*$^{-/-}$ progeroid mice; avoids muscle atrophy in C57BL/6 mice.	Krishnan et al., 2011; Walsh et al., 2015
D-glucosamine (glycolysis inhibitor)	increases mitochondrial biogenesis; reduces blood glucose; increases amino acid catabolism.	Weimer et al., 2014
Methionine restriction	activates H_2S production via transsulfuration; exerts protective effects in ischemia reperfusion injury.	Hine et al., 2015; Sanchez-Roman and Barja, 2013
Metformin	improves physical performance; reduces plasma LDL and cholesterol levels; alleviates hepatic steatosis and diabetes induced by high-fat diet.	Martin-Montalvo et al., 2013; Song et al., 2015
Nicotinamide mononucleotide	elevates NAD^+ levels; enhances abundance and function of respiratory chain complexes.	Gomes et al., 2013
Protein restriction	improves cardiometabolic health; reduces plasma levels of branched amino acids.	Solon-Biet et al., 2014
Rapamycin	protects against high-fat diet-induced obesity; reverses cardiac decline; improves immune function; delays neurodegeneration in a mouse model of AD; exhibits superior lifespan-extending activity in female mice.	Johnson et al., 2013;Li et al., 2014; Lin et al., 2015; Mannick et al., 2014
Resveratrol	reduces adipocyte size; stimulates SIRT1 expression; inhibits NF-kB activation; ameliorates insulin sensitivity; shows similar effects in rhesus monkeys.	Baur et al., 2006; Jimenez-Gomez et al., 2013; Liu et al., 2012; Mattison et al., 2014
Spermidine	improves aortic pulse wave velocity; reduces striatal toxicity of nitroproprionic acid; avoids salt-induced hypertension; postpones cardiac aging.	Jamwal and Kumar, 2016; LaRocca et al., 2013
Tryptophan restriction	delays age-associated tumor onset; reduces ischemia/reperfusion damage of kidney and liver.	Peng et al., 2012

Abbreviations: AD, Alzheimer's disease; FGF21, fibroblast growth factor 21; IGF1, insulin-like growth factor 1; LDL, low-density lipoprotein; SIRT1, sirtuin 1; Zmpste24, zinc metallopeptidase, STE24.

biochemical effects of CR but do not provoke a sizeable weight loss. In addition, drugs like rapalogs (which are MTOR inhibitors) and metformin (which mediates various effects including the activation of AMPK) are being proposed for the general treatment of age-associated disorders (Table 1 and Figure 2). Interestingly, the lifespan-extending effects of some of these interventions exhibit considerable sexual dimorphism (Harrison et al., 2014). The reasons underlying such a gender bias remain to be elucidated.

Caloric Restriction

CR, which can be defined as a reduced intake of calories not causing malnutrition, is the sole intervention that can prolong longevity in all species that have been investigated so far, from yeast to non-human primates (Madeo et al., 2015). Weight reduction by CR confers functional benefits by alleviating the physical complications of obesity, including excess intramuscular adipose tissue and joint overload. Beyond these mechanic aspects, CR eliminates white adipose tissue, in particular visceral fat—which is particularly noxious for healthy aging due to its pro-inflammatory and diabetogenic activity—and increases metabolic flexibility (Finkel, 2015). Moreover, CR constitutes an efficient inducer of autophagy in human tissues, and this has multiple anti-aging effects as it promotes efficient quality control on organelles, supports optimal stem cell activity, improves immunological functions, and inhibits malignant transformation (Galluzzi et al., 2015). Proficient autophagic responses also ameliorate several aspects of age-associated diseases, including arteriosclerosis, neurodegeneration, hepatic steatosis, and type 2 diabetes (Levine and Kroemer, 2008).

CR triggers beneficial autophagic responses through nutrient sensors like SIRT1, AMPK, and MTORC1 (Galluzzi et al., 2014), and such responses appear to be coupled to the activation of FOXO1, which also preserves telomerase activity (Makino et al., 2016). In this setting, SIRT1 is activated upon increased NAD^+ availability (which also occurs during physical exercise), whereas AMPK and MTORC1 mainly respond to dwindling ATP concentrations and amino acid depletion, respectively. As discussed above, autophagy is required for lifespan extension by CR in multiple model organisms. In *C. elegans*, the autophagy-dependent beneficial effect of CR on longevity strictly requires the nematode ortholog of SIRT1. In mice, the brain-specific overexpression of Sirt1 suffices to increase lifespan (Madeo et al., 2015). However, it has not been determined whether CR and the genetic induction of autophagy are epistatic with respect to their anti-aging effects in mammals.

CR causes hepatocytes to release the hormone fibroblast growth factor 21 (Fgf21), which participates in the adaptive response to starvation by stimulating hepatic fatty-acid oxidation and ketogenesis as it locally inhibits GH1/IGF1 signaling. Transgenic expression of *Fgf21* is sufficient to extend lifespan

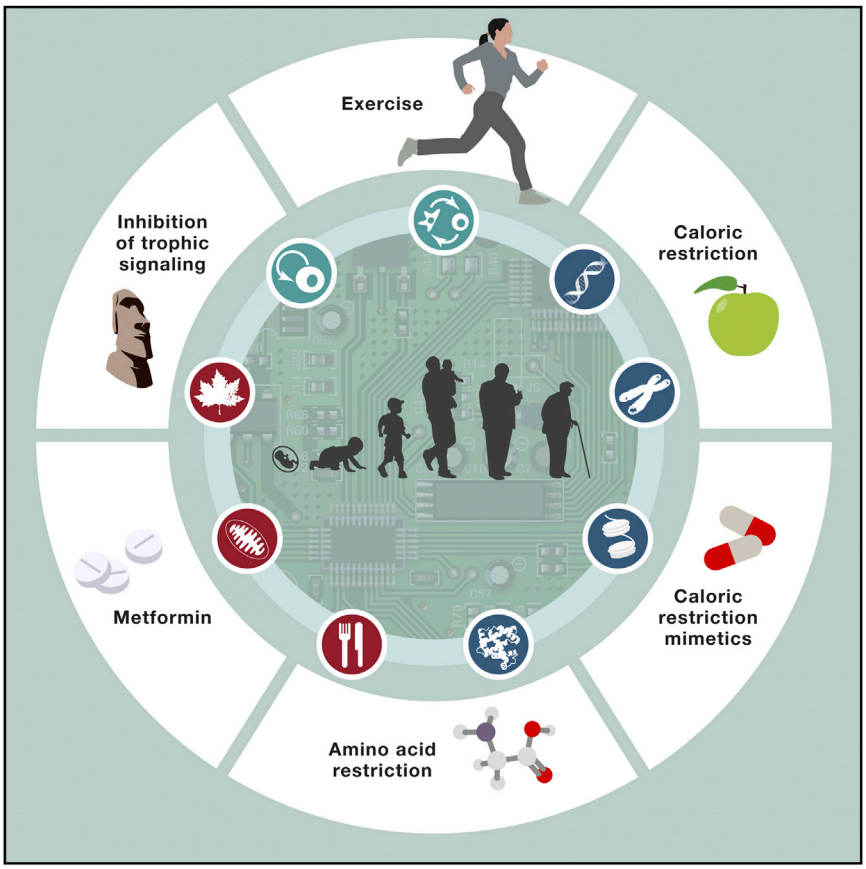

Figure 2. Metabolic Interventions that Improve Longevity

Data from several model organisms indicate that aging and the manifestations of age-associated disorders can be delayed by regular exercise, caloric restriction, small molecules that mimic the effects of fasting but are not associated with a sizeable weight loss (caloric restriction mimetics), limited intake of amino acids, inhibition of trophic signal-transduction cascades (for instance, with rapamycin, originally discovered in Rapa Nui island), and metformin (an antidiabetic drug with pleiotropic metabolic effects). Possibly, these interventions may also extend human lifespan.

in mice (Zhang et al., 2012). CR also stimulates an increase in the plasma levels of insulin-like growth factor binding protein 1 (IGFBP1) in non-obese adults, thereby reducing the concentrations of bioavailable IGF1 (Fontana et al., 2016). Voluntary CR mediates anti-inflammatory effects by promoting the release of cortisol in the bloodstream (Yang et al., 2016), by increasing the circulating concentrations of ketone bodies including β-hydroxybutyrate, which activates FOXO3A (Shimazu et al., 2013), and by directly inhibiting the NLRP3 inflammasome (Youm et al., 2015). Moreover, CR activates SIRT3 and hence limits age-associated tissue fibrosis (at least in mice), presumably by hyperacetylating and inhibiting glycogen synthase kinase 3 beta (GSK3B) (Sundaresan et al., 2015). Notably, in a clinical trial involving healthy volunteers, a starvation period of as little as 24 hr reduced NLRP3 activation in circulating leukocytes, and this re-augmented upon re-feeding paralleled by SIRT3 inhibition (Traba et al., 2015).

Although these observations may be blended into the simple hypothesis that continuous CR improves healthspan and extends longevity through a series of cellular and neuroendocrine effects, some aspects of CR remain perplexing. Periodic cycles of CR (e.g., fasting on alternate days, which does not lead to body-weight loss) are sufficient to extend longevity in rodents (Longo and Mattson, 2014). Intermittent fasting and exercise increase the expression of brain-derived neurotrophic factor (Bdnf) in several regions of the rodent brain, and this may mediate local and systemic anti-aging effects as Bdnf enhances synaptic plasticity, promotes neurogenesis, increases the resistance of neurons to cell death, regulates appetite, augments peripheral glucose metabolism, and ameliorates the autonomic control of cardiovascular and gastrointestinal systems. However, intermittent fasting is expected to have additional effects on the central nervous system and other organs that affect longevity. Indeed, intermittent fasting prevents ischemic damage in several organs, slows down neurodegeneration in multiple rodent models, and prevents or ameliorates the outcome of epileptic seizures and neurotrauma (Longo and Mattson, 2014). These beneficial effects correlate with increased antioxidant capacity, neurotrophic factor secretion, protein chaperones availability, and reduced pro-inflammatory cytokines. Interestingly, most of these neurological conditions are also mitigated by autophagy. However, the possibility that CR counteracts neurodegeneration via autophagy induction has not been investigated.

Importantly, restricting access to food for a few hours per day is sufficient to improve health and longevity in mice. Thus, although mice under time-restricted high-fat diet (such as 8 hr during the dark phase only or 4 hr during the light phase only) take up as much calories as mice with ad libitum access to food, they are protected against obesity, hepatic steatosis, and hyperinsulinemia (Asher and Sassone-Corsi, 2015). Mice kept on an unhealthy high-sugar or high-fat diet combined with daily fasting intervals outcompete non-fasting mice kept on regular chow in endurance tests, suggesting that breaks in between meals may actually be more important than the quality of food (Chaix et al., 2014). In *Drosophila melanogaster*, CR increases the amplitude of cycling in most circadian clock genes, and knockout of the core circadian clock genes (*tim* and *per*) abolishes lifespan extension by CR (Katewa et al., 2016). Of note, circadian clocks are modulated by major regulators of autophagy, including AKT1, MTOR, and sirtuins (Masri et al., 2014). Moreover, hypothalamic pacemaker neurons are regulated by the starvation hormone Fgf21, at least in mice. However, the molecular hierarchy between autophagy and circadian clocks has not been established thus far.

Protein and Amino Acid Restriction

Selective protein restriction leads to a reduction in serum IGF1 levels in humans aged 50–65 years, an effect that is associated with a reduced incidence of cancer and all-cause mortality (Levine et al., 2014). Of note, such a reduction in circulating IGF1 is not mediated by global CR (Fontana et al., 2016). Extensive studies on the links between macronutrients and lifespan in mice have confirmed that health and longevity are supported by the replacement of proteins with carbohydrates (Solon-Biet et al., 2014). An isocaloric dietary regimen characterized by the selective depletion of a single amino acid, methionine, can extend longevity in multiple model organisms from yeast to rodents (Madeo et al., 2015). Dietary methionine is in equilibrium with SAM, which is an essential donor of methyl groups for DNA methyltransferases and hence influences epigenetic processes. The acceleration of SAM catabolism by transgenic expression of glycine *N*-methyltransferase (*Gnmt*) extends the lifespan of flies and may represent a longevity-extending measure alternative to inhibitors of SAM synthesis (Obata and Miura, 2015). Methionine restriction has also been shown to promote the cystathionase (Cth)-dependent synthesis of hydrogen sulfide (H_2S), which is required for lifespan extension by CR (Hine et al., 2015). Interestingly, H_2S can also activate autophagy, highlighting yet another link between methionine restriction and autophagy induction.

Attempts are ongoing to create dietary regimens that can be consumed ad libitum as they contain reduced amounts of calories and proteins, as this applies to the so-called "fasting-mimicking diet" (FMD). When given periodically (for 4 days twice a month, with standard chow in the intervals) to middle-aged mice, the FMD lowers visceral fat, reduces cancer incidence, rejuvenates the immune system, limits aging-associated skin lesions and autophagic defects in muscles, retards bone mineral density loss, and extends longevity. When fed to aged mice, the FMD also lowers circulating IGF1 levels, promotes hippocampal neurogenesis, and improves cognitive performance. When administered to patients (for 5 days per month, over 3 months), an FMD covering 44% ± 10% of the average caloric intake and containing 10% of proteins reduced baseline glucose, circulating IGF1 and C-reactive protein (Brandhorst et al., 2015). These findings illustrate the possibility of generating new dietary formulations that mediate the benefits of CR but may be perceived as more agreeable than CR.

Caloric Restriction Mimetics

CRMs resemble CR in their ability to deplete the nucleocytosolic pool of acetyl-CoA, thereby limiting substrate availability to multiple acetyltransferases including E1A-binding protein p300 (EP300), activate SIRT1 and AMPK, and inhibit MTORC1 (Eisenberg et al., 2014; Mariño et al., 2014). The direct inhibition of enzymes that generate nucleocytosolic acetyl-CoA (such as ATP citrate lyase, ACLY), the blockade of acetyltransferases, or the activation of SIRT1 are sufficient to activate AMPK and to inhibit MTORC1, with the subsequent induction of autophagy as a lifespan-extending mechanism (Mariño et al., 2014). Depletion of acetyl-CoA extends the survival of yeast cells, provided that they are autophagy competent (Eisenberg et al., 2014). Similarly, the acetyl-CoA-depleting drug hydroxycitrate improves immunosurveillance against autophagy-competent cancer cells in mice (Pietrocola et al., 2016). Moreover, the EP300 inhibitor spermidine and the SIRT1 activator resveratrol only extend the lifespan of nematodes that harbor an intact autophagic machinery (Madeo et al., 2015). Resveratrol and SRT1720 (another activator of SIRT1) prolong the healthspan and longevity of obese mice, an effect that is accompanied by improved insulin sensitivity, elevated mitochondrial content, decreased inflammation, ameliorated motor coordination, and increased bone mineral density (Mitchell et al., 2014). SRT1720 and SRT2104 (yet another SIRT1 activator) have similar effects on mice maintained on standard diet. However, it remains to be elucidated whether the ability of SIRT1 activators to extend lifespan in mammals depends on autophagy.

As mentioned above, the detrimental effects of PARP1 hyperactivation can be reversed by external supply of nicotinamide riboside, which activates SIRT1. Another NAD^+ precursor (nicotinamide mononucleotide) can ameliorate the negative effects of partial NAD^+ depletion resulting from defects in the mitochondrial respiratory complex 1, thereby avoiding heart failure through the activation of the mitochondrial SIRT3 (Karamanlidis et al., 2013). These findings support the use of NAD^+ precursors to limit premature aging caused by mitochondrial disorders (Cerutti et al., 2014). Similarly, the exogenous supply of nicotinamide riboside or nicotinamide mononucleotide can increase lifespan in *C. elegans* through activation of the nematode ortholog of SIRT1, induction of the UPR^{mt}, or activation of DAF-16 (Mouchiroud et al., 2013). Similar findings have been obtained upon the administration of the PARP1 inhibitor olaparib, suggesting that another approach to increasing NAD^+ levels may consist of the inhibition of NAD^+-consuming enzymes. Accordingly, pharmacological inhibition of Parp1 avoids the detrimental effects on metabolism imposed by high-fat and high-sucrose diets (Pirinen et al., 2014). However, it is unlikely that such manipulations would be possible in humans, based on the critical requirement of PARP1 for DNA repair.

Spermidine can extend the lifespan of both non-mammalian model organisms and rodents (Madeo et al., 2015). A similar effect can be obtained by feeding mice with bacteria plus arginine, resulting in the production of high levels of polyamines in the intestine (Kibe et al., 2014). Spermidine mediates broad beneficial effects in aging rodents, including a reduction in arterial stiffness and an improved regeneration of skeletal muscles (LaRocca et al., 2013). This latter phenomenon is abrogated by the muscle satellite cell-specific deletion of *Atg7* (encoding a critical component of the autophagic machinery) and may result from the autophagy-dependent suppression of cellular senescence (García-Prat et al., 2016). Oral spermidine supplementation can also avoid neurodegeneration in mice, further underscoring the broad protective effects of this natural polyamine.

It has recently been shown that EP300 can acetylate the microtubule-associated protein tau (Mapt), hence reducing its turnover and provoking its accumulation in fibrils that are common in Alzheimer's disease and frontotemporal dementia (Min et al., 2015). The EP300-mediated acetylation of Mapt can be inhibited in vitro by salicylate (the active principle of aspirin) and salsalate (a prodrug of salicylate that crosses the brain-blood barrier). In line with this notion, salsalate delays the onset of neurodegeneration in a mouse model of frontotemporal dementia

(Min et al., 2015). Intriguingly, aspirin can extend the lifespan of genetically heterogeneous male mice (Strong et al., 2008). However, it remains to be clarified whether this effect reflects the ability of salicylate to inhibit EP300, activate AMPK, or exert anti-inflammatory and oncopreventive effects upon the inhibition of prostaglandin-endoperoxide synthase 2 (PTGS2; best known as COX2).

Inhibition of Trophic Signal-Transduction Pathways

A more specific way to mimic the effects of CR consists in the interruption of signal-transduction cascades that promote anabolic reactions, including the IIS. This objective has been achieved in *Drosophila* by inhibiting two parallel pathways operating downstream of INSR and the IGF1 receptor (IGF1R), namely, (1) the PI3K-AKT1-FOXO cascade and (2) the RAS-ERK-AOP cascade (Slack et al., 2015). Along similar lines, the pharmacological inhibition of PI3K diminishes adiposity and metabolic syndrome in obese mice and rhesus monkeys (Ortega-Molina et al., 2015) but has not yet been shown to extend lifespan in normal mice. AKT1 phosphorylates and activates ACLY, which explains why AKT1 inhibitors cause a decrease in protein acetylation (Lee et al., 2014). However, the mechanistic relationship between these effects and aging has not been elucidated. Interestingly, the $Myc^{+/-}$ genotype, which reduces PI3K-AKT1-MTOR signaling, is sufficient to extend mouse longevity (Hofmann et al., 2015). Likewise, transgenic mice expressing additional copies of phosphatase and tensin homolog (*Pten*) exhibit an increased energy expenditure, are protected from metabolic pathologies, and live longer than their wild-type littermates. All these beneficial effects can be recapitulated by a synthetic PI3K inhibitor (Ortega-Molina et al., 2012). Altogether, these observations suggest that distinct manipulations that limit anabolism or stimulate non-toxic catabolism have a concordant effect on healthspan and lifespan.

CR and CRMs inhibit MTOR, and direct inhibition of MTORC1 signaling by rapamycin or similar compounds (rapalogs) extends lifespan in worms, flies, and mice. Aged mice from 12 different genotypes fed with chow containing 14 ppm rapamycin exhibited a significant lifespan extension as compared to control mice (Harrison et al., 2009). However, similar doses of rapamycin limited lifespan in transgenic mice bearing a mutant form of superoxide dismutase 1 (Sod1) that causes a motoneuron degeneration syndrome resembling human amyotrophic lateral sclerosis (Zhang et al., 2011), as well as in C57BL/KsJ-$Lepr^{db/db}$ mice, which spontaneously develop obesity and type 2 diabetes (Sataranatarajan et al., 2016). That said, rapamycin improves cognition and prevents neurodegeneration in various mouse models, ameliorates cardiac function in aging mice, suppresses senescence-associated inflammation, and mediates immunosuppressive effects that are clinically harnessed for the prevention of solid graft rejection (Shimobayashi and Hall, 2014). Curiously, and despite its anti-inflammatory and immunosuppressive properties, rapamycin can rejuvenate immune stem cell function (Chen et al., 2009). It is also somewhat counterintuitive that prolonged (20 weeks) intraperitoneal rapamycin ameliorates metabolic profile, oxygen consumption, ketogenesis, and insulin sensitivity in mice, whereas short-term (2 weeks) rapamycin has detrimental effects on metabolism (Fang et al., 2013).

The beneficial effects of rapamycin can be phenocopied in female mice by deletion of ribosomal protein S6 kinase 1 (*Rps6kb1*, coding for an MTOR target), a maneuver that also increases longevity (Selman et al., 2009), as well as by artificial induction of autophagy (see above). In flies, the lifespan-extending effects of rapamycin are lost upon inactivation of autophagy (Madeo et al., 2015), but such a mechanistic study has not been performed in mice thus far. Of note, some of the positive outcomes of MTORC1 inhibition involve intercellular communication. This has been demonstrated in intestinal stem cells, whose function is improved by MTORC1 inhibition in Paneth cells (Yilmaz et al., 2012). Likewise, short-term CR increases the number and regenerative potential of muscular stem cells in mice as it favors the establishment of a microenvironment that supports homeostatic stem cell metabolism and ameliorates their resistance to stress (Cerletti et al., 2012). Therefore, strategies aimed at preserving or even increasing the functional activity of the stem cell niche may be key components of future anti-aging approaches.

Metformin

Activation of AMPK by metformin initiates a neuroendocrine duodenal pathway that eventually reduces hepatic glucose production in rats (Duca et al., 2015). At least partially, this effect may stem from the ability of metformin to inhibit solute carrier family 22 member 1 (SLC22A1; best known as OCT1), hence limiting OCT1-dependent thiamine uptake (Chen et al., 2014). Metformin also affects folate and methionine metabolism in *Escherichia coli*, and *C. elegans* fed with metformin-treated bacteria experience methionine restriction and consequent lifespan extension (Cabreiro et al., 2013). It is therefore possible—yet remains to be proven—that the positive effects of metformin in patients with type 2 diabetes are linked to an increased abundance of *Escherichia spp.* within the gut microbiome, resulting in the abundant production of short-chain fatty acids, such as butyrate and propionate, with beneficial activity (Canfora et al., 2015). The changes imposed by metformin on the microbiome might result from taxon-specific resistance/sensitivity to the bacteriostatic or microbicide properties of the drug, as well as from effects on intestinal lipid absorption or local inflammatory reactions (Forslund et al., 2015). It appears therefore plausible that metformin mediates part of its antidiabetic and enigmatic anticancer effects through alterations in the microbiome, which has a central role in healthy aging. In view of the safety profile and pharmacodynamic properties of metformin, the Targeting Aging with Metformin (TAME) clinical trial—a first-in-class study enrolling patients who have been diagnosed with one single age-associated condition and designed to detect the capacity of metformin to delay the manifestation of a second, equally age-associated disorder—is currently being planned.

Exercise

In humans, physical fitness and longevity are strongly associated, consistent with the common observation that regular exercise reduces morbidity and mortality in humans (Neufer et al., 2015). In normal mice, spontaneous exercise does not prolong lifespan but does extend healthspan. Forced endurance exercise on a treadmill can improve the deterioration of the brain metabolome in progeroid $Polg^{D257A/D257A}$ mice. In this setting, deficits in the neurotransmitters acetylcholine, glutamate, and

Table 2. Obesity as an Aging Accelerator

Aging Hallmark	Observations	References
Genomic instability	lymphocytes from obese children exhibit increased incidence of DNA damage.	Scarpato et al., 2011
Telomere attrition	signs of metabolic syndrome correlate with reduced telomere length; weight gain correlates inversely with telomere length; telomere length increases after bariatric surgery of obese patients.	Laimer et al., 2016; Müezzinler et al., 2016; Révész et al., 2015
Epigenetic alterations	The epigenetic clock is advanced by obesity in the liver; the transcriptomic age of leukocytes is higher than chronological age in obese individuals; spermatozoa from obese men carry a distinctive DNA methylation signature.	Horvath et al., 2014; Peters et al., 2015
Loss of proteostasis	high-fat diet inhibits autophagy in hepatocytes and macrophages; obese and diabetic mice expressing mutant $Mapt^{P301L}$ exhibit an accelerated tauopathy.	Koga et al., 2010; Liu et al., 2015; Platt et al., 2016
Deregulated nutrient sensing	adipose tissue inflammation impairs glucose metabolism and causes diabetes; obesity is associated with reduced NAD^+ levels and SIRT1 inhibition; obesity causes AMPK inhibition and mTORC1 activation in multiple cell types.	Brestoff and Artis, 2015; Fu et al., 2016; Jukarainen et al., 2016; Umemura et al., 2014
Mitochondrial dysfunction	reduced metabolic flexibility; increased acetyl-CoA load, but reduced NAD^+ levels with inhibition of mitochondrial sirtuins; increased mitochondria-associated ER membranes in liver; reduced mitochondrial biogenesis in adipose tissue that improves upon bariatric surgery.	Arruda et al., 2014; Heinonen et al., 2015; Jahansouz et al., 2015; Muoio, 2014)
Cellular senescence	obesity is associated with an increase in senescence markers, inflammatory cytokines, and DNA damage foci in adipocytes; deoxycholic acid, an obesity-induced gut microbial metabolite, induces senescence in liver cells.	Escande et al., 2014; Tchkonia et al., 2010; Yoshimoto et al., 2013
Stem cell exhaustion	reduced frequency of neural stem cells; reduced hematopoietic stem cells in bone marrow.	Li et al., 2012; Luo et al., 2015
Altered intercellular communication	enhanced inflammation in gut and adipose tissues; increased hypothalamic TGF-β1 production; reprogrammed circadian rhythms.	Eckel-Mahan et al., 2013; Nagareddy et al., 2014; Odegaard and Chawla, 2013; Yan et al., 2014

Abbreviations: AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; Mapt, microtubule-associated protein tau; MTORC1, mechanistic target of rapamycin complex 1; SIRT1, sirtuin 1; TGF-β1, transforming growth factor beta 1.

aspartate, as well as depletion of NAD^+ and carnitine metabolites, were largely normalized by exercise, which also decreased acetyl-CoA levels (Clark-Matott et al., 2015). Depletion of the nucleocytosolic acetyl-CoA pool stimulates autophagy (Mariño et al., 2014), and exercise has indeed been shown to improve metabolism and antagonize high-fat diet-induced diabetes through the induction of autophagy. Exercise also reduces mitochondrial protein acetylation, which may facilitate organelle quality control by mitophagy (Overmyer et al., 2015), and upregulates PGC1α, hence counteracting its age-related decline. Accordingly, PGC1α is sufficient and necessary for preventing muscle atrophy and to retain mitochondrial content and function in aging mice (Hood et al., 2015).

Altogether, the beneficial effects of exercise involve all nine hallmarks of aging. It seems therefore unlikely that the induction of one (or a few) metabolic effects of physical activity may constitute a "gymnomimetic" strategy (Burke et al., 2010). Nonetheless, exercise increases the circulating levels of the NAD^+ precursor nicotinamide (Lewis et al., 2010), which has a positive impact on aging-related conditions (see above). Moreover, high-intensity exercise resembles fasting in its ability to increase the plasma concentration of β-hydroxybutyrate, which also exerts multipronged anti-aging effects. Hence, the health benefits of exercise and CR partially overlap.

Westernized Lifestyle—An Aging Accelerator

The so-called westernized lifestyle is characterized by an accrued calorie intake coupled to the omission of healthy food (e.g., vegetables, fruit, fibers, etc.) from common dietary habits and sedentariness. During the past two centuries, the overall quality of life and longevity in Western countries have undoubtedly been enhanced. However, the ever-expanding epidemic of obesity and co-morbidities may annihilate the health benefits of modern civilization. Together with elevated blood pressure, supraphysiological plasma glucose in fasting conditions, high serum triglycerides, and low high-density lipoprotein levels, obesity (especially abdominal obesity) is one of the manifestations of metabolic syndrome. Importantly, the prevalence of all these signs, as well as that of sarcopenia (the degenerative loss of skeletal muscles) increases with age. Obesity is a major risk factor for multiple aging-associated diseases including arteriosclerosis, cancer, and neurodegenerative disorders (Dietz et al., 2015). Similarly, type 2 diabetes predisposes to vascular and non-vascular dementia (Chatterjee et al., 2016). Even a transient phase of obesity in an individual's history predisposes to diabetes and cardiovascular disease (and associated mortality), suggesting that the actual weight of obesity laying on the society is being underestimated.

Accumulating evidence indicates that genetic predisposition to longevity is associated with low levels of abdominal visceral fat (Sala et al., 2015). Moreover, many different manipulations that prolong lifespan in model organisms also improve obesity-related conditions. The adenoviral delivery of *Atg7* to the livers of obese mice efficiently induces autophagy as it restores insulin/glucose homeostasis and reduces ER stress (Yang et al., 2010), whereas transgenic expression of *Tfeb* in the liver protects mice from the

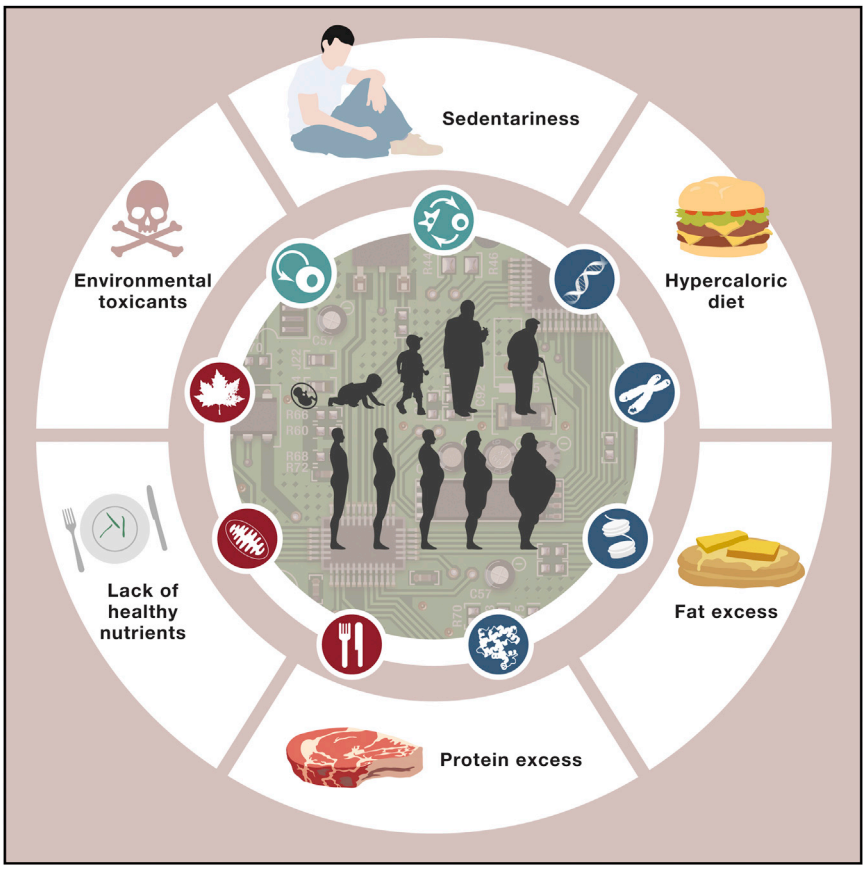

Figure 3. Impact of Westernized Lifestyle on Human Longevity

Accumulating experimental and epidemiological evidence suggests that the aging process and the manifestations of age-associated pathologies are accelerated by various aspects of the so-called "westernized lifestyle," including a hypercaloric diet associated with excess fat and protein intake but limited amount of healthy food, exposure to environmental toxicants from the food industry, and an exaggerated sedentariness.

hepatotoxic effects of high-fat dietary regimens (Settembre et al., 2013). Agents that stimulate autophagy, such as rapamycin and spermidine, also prevent steatohepatitis and obesity in mice on high-fat diet (Kim and Lee, 2014). Likewise, nicotinamide riboside prevents steatohepatitis induced by a high-fat and high-sucrose diet, a protective effect that requires Sirt1 expression by hepatocytes and might involve the UPR^{mt} (Gariani et al., 2016). Conversely, defects in the molecular machinery for autophagy such as those imposed by the *Atg4b*$^{-/-}$, *Atg7*$^{+/-}$, or *Becn1*$^{+/-}$ genotypes are sufficient to favor the accumulation of intracellular lipids in the livers of wild-type mice maintained on a high-fat diet or spontaneously hyperphagic *ob/ob* mice, a steatotic response that is accompanied by enhanced systemic inflammation and development of type 2 diabetes (Lim et al., 2014).

These observations strongly suggest that aging and obesity—with their overlapping co-morbidities—are regulated by similar pathways. Consistent with this hypothesis, epidemiological and interventional studies demonstrate that obesity accelerates each of the nine hallmarks of aging (Table 2 and Figure 3). Accordingly, hypernutrition favors systemic inflammation, dysregulation of adipokines, insulin resistance, dysbiosis, and immune system alterations. Perhaps the most striking observations in this regard are that obesity is linked to telomere shortening, and that drastic measures to combat morbid obesity like bariatric surgery can actually cause a recovery in LTL (Laimer et al., 2016).

The molecular mechanisms through which obesity accelerates aging are presumably linked to its metabolic effects. For example, it has been observed that obesity causes depletion of NAD^+ coupled to sirtuin inactivation (Kraus et al., 2014). Accordingly, knockout of nicotinamide N-methyltransferase (*Nnmt*) in the liver and white adipose tissue enhances local NAD^+ levels and protects animals against diet-induced obesity (Kraus et al., 2014). Conversely, the transgene-driven overexpression of *Nnmt* in primary hepatocytes increases the production of the SIRT1-stabilizing nicotinamide derivative N(1)-methylnicotinamide (MNAM), and this has beneficial effects on cholesterol and triglyceride levels in mice on high-fat diet (Hong et al., 2015). Thus, whether Nnmt has positive or negative effects on obesity remains to be clarified.

Pharmacological activation of sirtuins also greatly improves the healthspan and lifespan of mice on high-fat dietary regimens. Along similar lines, inactivation of Sirt1 or Dbc1 (a HDAC3 inhibitor) avoids the premature senescence of adipocytes and the manifestations of metabolic syndrome (Escande et al., 2014). Metabolic sensors other than SIRT1 are perturbed in obese individuals. For example, the inhibition of AMPK in satellite cells is responsible for reduced skeletal muscle regeneration, a condition that might contribute to age-associated sarcopenia (Fu et al., 2016), whereas chronic activation of MTORC1 may contribute to the hepatic steatosis that often accompanies aging (Umemura et al., 2014). However, other aging-accelerating effects of obesity may be mediated through rather indirect mechanisms.

The westernized lifestyle is also associated with nutritional exposure to specific environmental toxicants. Examples include advanced glycation end-products (AGEs), which are generated by food overheating. Correlative studies in humans and interventional studies in mice indicate that *N*-(carboxymethyl)lysine and methylglyoxal derivatives of glucose-protein or glucose-lipid interactions—which serve as markers for AGEs—accumulate in tissues and accelerate several manifestations of aging, including cognitive decline and metabolic syndrome (Cai et al., 2014). Similarly, *trans*-fatty acids—which are prevalent in margarines

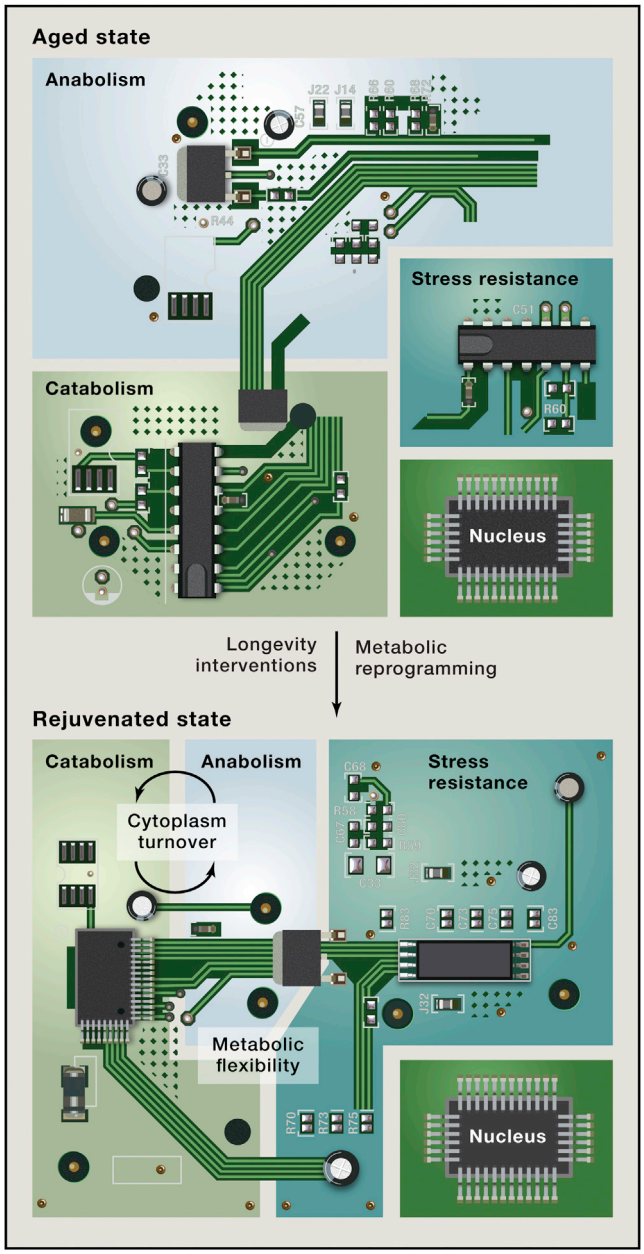

Figure 4. Metabolic Reprogramming and Longevity
Anti-aging interventions cause a global metabolic rewiring that is associated with the redistribution of nutrients from anabolic metabolism supporting cell growth and proliferation to catabolic reactions that enhance cytoplasmic turnover, metabolic flexibility, stress resistance, and homeostasis maintenance.

and manufactured cooking oils as a result of the industrial hydrogenation of unsaturated fatty acids—are reputed to be toxic. Thus, the plasma levels of phospholipids *trans*-16:1n9 and *trans*-18:1 are positively associated with type 2 diabetes (Wang et al., 2015), and the intake of both *trans*-unsaturated and *trans*-saturated fatty acids correlates with an increased risk of cardiovascular disease. Moreover, naturally occurring *trans*-fatty acids from ruminants—such as vaccenic acid—have a negative impact on cholesterol levels, as determined in a double-blind, randomized, crossover feeding trial enrolling 106 healthy adults (Gebauer et al., 2015). The consumption of red meat and high-fat dairy products predisposes to developing aging-related pathologies such as ischemic heart disease, colorectal cancer, and type 2 diabetes. Fructose contained in common sodas favors hepatic lipid synthesis, visceral adiposity, and metabolic syndrome (Malik and Hu, 2015). Moreover, dietary emulsifiers and other additives used in the food industry have a negative impact on the gut microbiota, hence promoting intestinal inflammation and metabolic syndrome (at least in mice) (Chassaing et al., 2015). Altogether, these observations suggest that the ingestion of toxic dietary compounds may further accelerate age-associated disorders in the context of a westernized lifestyle.

Conclusions

Aging complicates the maintenance of cellular and organismal metabolic homeostasis, hence favoring an imbalance in metabolic landscape that self-amplifies and eventually becomes clinically manifest. Thus, all the anti-aging interventions discussed above may operate in the context of a metabolic reprogramming that (1) ensures efficient nutrient utilization and (2) enhances stress resistance. Although such a metabolic reprogramming may be extremely broad and hence difficult to modulate pharmacologically, it may be subjected to some unifying principles. In particular, the signal-transduction cascades and metabolic circuitries rewired in the course of aging may operate in the context of a limited number of modules that redistribute nutrients and other resources from anabolism to non-toxic catabolism, hence favoring homeostasis preservation (Figure 4). This is well exemplified by the longevity-extending effects of several distinct maneuvers that inhibit IIS or activate autophagy.

That said, some caveats should be taken into careful consideration when aging and longevity are placed in the context of a systemic rewiring of intermediate metabolism. First, a sizable fraction of the aforementioned studies have been performed in *C. elegans* or *D. melanogaster* and have not yet been validated in mammals. Second, consistent molecular biomarkers of aging are lacking, which considerably complicates the assessment of the short- and long-term consequences of metabolic interventions on the aging process. Third, none of the longevity-extending interventions described above has been demonstrated to delay the onset or progression of age-associated disorders in humans. We are positive that the concerted study of aging and metabolism will provide novel insights into the aging process, which will be instrumental to the development of clinically implementable strategies of healthspan and lifespan extension. Organizations like the National Institute on Aging Interventions Testing Program (NIA-ITP), which are currently striving to homogenize the experimental models and procedures employed world-wide to study longevity, are expected to play a fundamental role in this setting.

Our current knowledge on the metabolic manipulations that may improve health in the elderly and hence extend longevity are still in their infancy, although there is no doubt that a combination of regular exercise and appropriate diet can delay the

onset and progression of all the hallmarks of aging. Formulating dietary recommendations is complicated, and personalized advice from a nutritionist may be recommendable in some situations. Nonetheless, we surmise that an increase in food-free intervals, a reduction in overall caloric and animal protein intake, as well as a general shift from health-compromising food to a Mediterranean diet rich in fibers and complex carbohydrates may have sizeable anti-aging effects, especially when combined with regular physical activity. The current tendency to adopt a westernized lifestyle all over the world is creating new health hazards that must be counteracted by public campaigns. Intriguingly, subjective well-being and positive affect are coupled to positive neuroendocrine, cardiovascular, and inflammatory parameters (Steptoe et al., 2014), confirming a tangible biological substratum for the long-suspected relationship between happiness and health. Hence, political actions that incentivize and democratize high-level education across social classes and, in addition, favor harmonious cooperation over ferocious competition among individuals might propagate healthy aging, thereby constituting the "ultimate preventative medicine" (Kaeberlein et al., 2015).

ACKNOWLEDGMENTS

We acknowledge all members of our laboratories for the support and constructive discussion during the elaboration of this manuscript, and we apologize for omission of relevant works and citations due to space constraints. C.L.-O. is supported by grants from Ministerio de Economía y Competitividad, Instituto de Salud Carlos III, and Botin Foundation (Spain). J.M.P.F. is supported by grants from Ministerio de Economía y Competitividad and Gobierno del Principado de Asturias (Spain). The Instituto Universitario de Oncología is supported by Fundación Bancaria Caja de Ahorros de Asturias. F.M. is supported by FWF grants LIPOTOX, I1000, P 27893, and P24381-B20, as well as by the BMWFW grant "Unconventional research." G.K. is supported by the Ligue contre le Cancer (équipe labelisée); Agence National de la Recherche (ANR) —Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Institut National du Cancer (INCa); Institut Universitaire de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the LeDucq Foundation; the LabEx Immuno-Oncology; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM); and the Paris Alliance of Cancer Research Institutes (PACRI).

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