Please cite this article in press as: Calubag et al., A nutrigeroscience approach: Dietary macronutrients and cellular senescence, Cell Metabolism (2024), https://doi.org/10.1016/j.cmet.2024.07.025

Cell Metabolism

CellPress

Review

A nutrigeroscience approach: Dietary macronutrients and cellular senescence

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https://doi.org/10.1016/j.cmet.2024.07.025

SUMMARY

Cellular senescence, a process in which a cell exits the cell cycle in response to stressors, is one of the hallmarks of aging. Senescence and the senescence-associated secretory phenotype (SASP)—a heterogeneous set of secreted factors that disrupt tissue homeostasis and promote the accumulation of senescent cells—reprogram metabolism and can lead to metabolic dysfunction. Dietary interventions have long been studied as methods to combat age-associated metabolic dysfunction, promote health, and increase lifespan. A growing body of literature suggests that senescence is responsive to diet, both to calories and specific dietary macronutrients, and that the metabolic benefits of dietary interventions may arise in part through reducing senescence. Here, we review what is currently known about dietary macronutrients' effect on senescence and the SASP, the nutrient-responsive molecular mechanisms that may mediate these effects, and the potential for these findings to inform the development of a nutrigeroscience approach to healthy aging.

INTRODUCTION

The population of the US is aging rapidly, and age-related diseases are placing great burdens on both families and the healthcare system.[1] Extending healthspan, the portion of life that is relatively free from major deficits that impair quality of life, by targeting aging directly may be an efficacious way to reduce these burdens.[2,3] Understanding the altered processes that drive aging is necessary to develop effective, translatable interventions to improve health and longevity.

One hallmark of aging is "cellular senescence," in which cells enter a largely irreversible, cell-cycle arrested state in response to stresses, especially that which induce DNA damage.[4–9] Senescence provides benefits early in life,[10] playing a role in development,[11–15] protecting against tumorigenesis,[16,17] and promoting wound healing and regeneration.[18–23] However, consistent with antagonistic pleiotropy (i.e., the mechanisms that were beneficial at a younger age become fatal as we age), detrimental effects of senescence are observed later in life.

An important component to maintain proper tissue homeostasis is preventing the accumulation of senescent cells (SnCs). Various immune cell types clear SnCs,[24] including M1 macrophages,[25–31] natural killer cells,[32–35] invariant natural killer T cells,[36] $CD8^+$ T cells,[35] and neutrophils.[19,24,25,37] These immune cells decline in function with age, which reduce immune clearance of SnCs in the aged.[25,37–41] The inflammatory senescence-associated secretory phenotype (SASP) of senescent-like immune cells drives systemic aging and paracrine senescence in non-immune tissues, resulting in chronic inflammation, tumor development, and tissue dysfunction (Figure 1).[42] For an in-depth review of SnC clearance by immune cells, see Kale et al.[25]

Senescence is tightly linked to aging, and SnC clearance through a transgenic approach delays the onset of several age-related diseases and extends the lifespan of progeroid and naturally aged mice.[43,44] SnCs can be selectively eliminated by pharmaceutical small molecules, termed senolytics, or their SASP suppressed by drugs termed senomorphics. Several senolytics have been shown to alleviate senescence-related phenotypes in pre-clinical models (e.g., dasatinib and quercetin [DQ], fisetin, and navitoclax).[38,45–53] For a full review on optimizing senotherapeutics to extend healthspan, see Robbins et al.[9]

Given the importance of identifying ways to promote healthy aging, attention has focused on dietary interventions such as calorie restriction (CR), which improves healthspan and extends lifespan in a diverse range of organisms.[54] CR prevents or slows multiple hallmarks of aging, including senescence.[55] This review will focus on nutritional modulation of senescence, as exciting new evidence suggests aging and age-related diseases driven by senescence can be regulated by diet. We will also highlight the potential nutrient-signaling pathways mediating the therapeutic effects on senescence. These findings offer the tantalizing possibility that we may be able to extend human healthspan through science-guided nutritional modulations that target a hallmark of aging.

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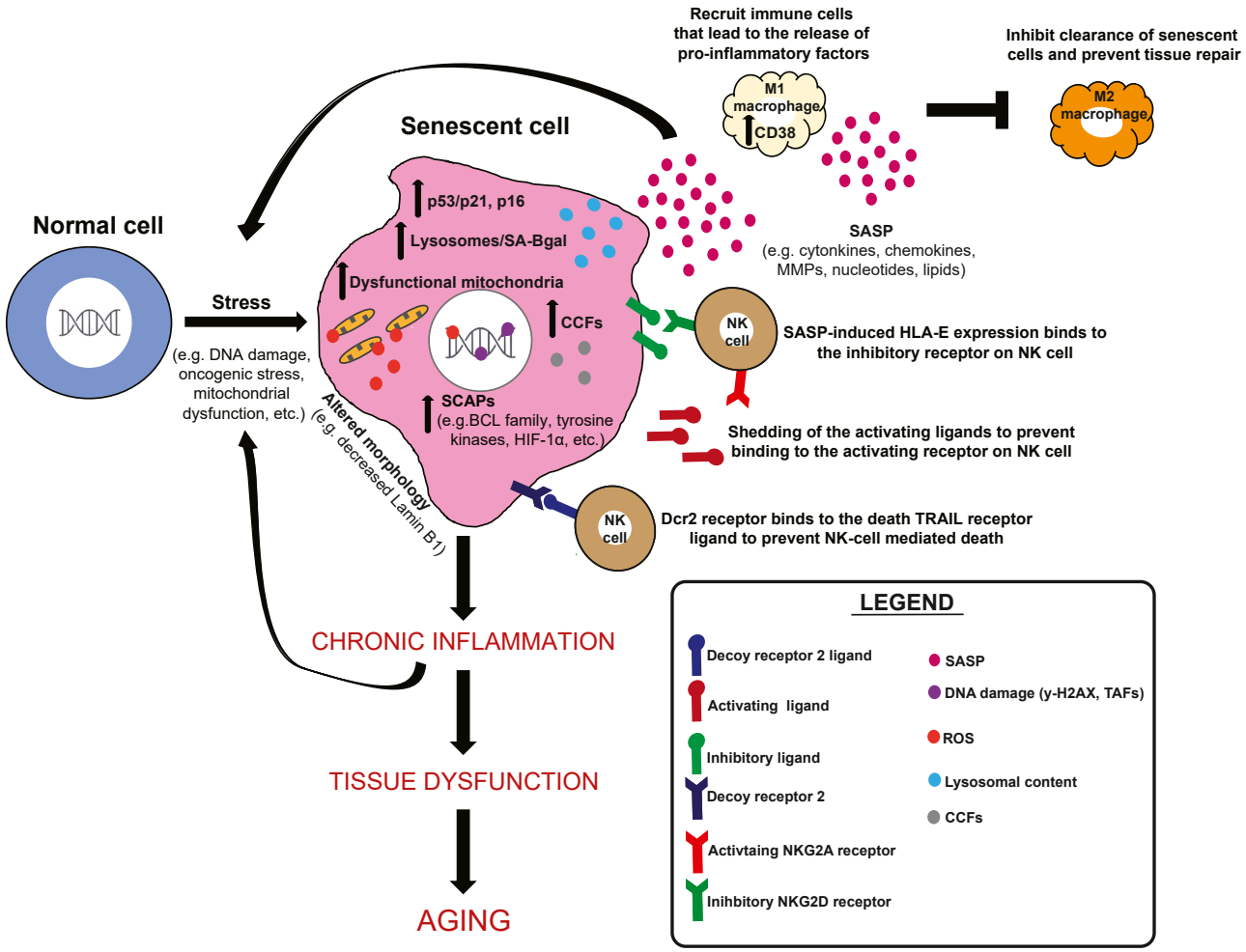


Figure 1. How cellular senescence alters cell function and promotes aging

When normal cells undergo some form of stressor, they can become senescent. In response to this damage, it causes cell-cycle arrest via the upregulation of the p53/p21 and p16 signaling pathways. Senescent cells (SnCs) release senescence-associated secretory phenotype (SASP), which is a mix of soluble factors that can reinforce senescence and induce senescence in nearby cells via paracrine senescence. The cell shape and content changes, such as decreased lamin B1 and increased lysosomal content. Decreased lamin B1 can lead to partitioning of the nuclear membrane into the cytoplasm as cytoplasmic chromatin fragments (CCFs), which can also promote SASP. Dysfunctional mitochondria can also lead to increased reactive oxygen species (ROS), which can induce senescence itself or reinforce the senescence phenotype. SnCs also upregulate senescent-cell anti-apoptotic pathways (SCAPs), such as HIF1a or the BCL family, to protect against apoptosis. SASP production recruits M1 macrophages to inhibit M2-mediate clearance of senescence. Senescent macrophages also trend toward an M1 phenotype rather than an M2, reinforcing senescence. SnCs also upregulate decoy receptor 2 (Dcr2) ligand expression and SASP-induced major histocompatibility complex histocompatibility antigen, alpha chain E, i.e., HLA-E, on their cell membrane as well as shed activating ligands from their cell membranes to prevent NK cell-mediated clearance. All these characteristics of senescence leads to chronic inflammation and tissue dysfunction promote age-related diseases.

CHARACTERISTICS OF CELLULAR SENESCENCE

The hallmarks of senescence include alterations in signaling pathways such as the DNA damage response, cell-cycle arrest, secretory phenotype, apoptosis resistance, metabolism, and endoplasmic reticulum stress as well as morphological alterations, such as cell size and shape, plasma membrane composition, increased lysosomal content, and mitochondria accumulation (Figure 1).[8,56] Here, we will discuss in greater depth specific characteristics of senescence.

Cell-cycle arrest

Over 60 years ago, Leonard Hayflick discovered that there is a finite lifespan to cultured human cells, termed "replicative senescence."[57] The main drivers of this cell-cycle arrest are the cyclin-dependent kinases inhibitors (CDKIs), including $p16^{INK4a}$ (p16, encoded by *CDKN2a*) and $p21^{CIP}$ (p21; encoded by *CDKN1a*).[56] Increased expression of p16, which can be activated by diverse stimuli including oxidative stress, DNA damage, and senescence itself, inhibits phosphorylated RB protein, leading to cell-cycle arrest via RB-mediated G1 checkpoint of the cell cycle to block entrance into the S-phase.[58] DNA damage that results in the phosphorylation of p53 upregulates p21, which also inhibits pRB.[58] Other CDKIs that contribute to senescence include $p15^{INK4b}$ and $p19^{INK4d}$, as well as the MDM2/p53 regulator $p14^{Arf}$ and its mouse homolog $p19^{Arf}$, but these alternative CDKIs have been significantly less used and studied as markers of senescence, as they arise from the

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same gene locus and potentially play redundant roles to p16.[58–61]

SASP

In 2008, the late Judith Campisi published her discovery and characterization of the SASP,[62] uncovering an entirely new side of senescence. SnCs produce a highly heterogeneous mix of cytokines, chemokines, metallomatrix proteins (MMPs), lipids, growth factors, metabolites, nucleic acids, and extracellular vesicles collectively called the SASP.[4,63,64] Common SASP components include: cytokines IL-1α, IL-1β, and IL-6; chemokines Cxcl1, ccl2/MCP1, and cxcl10; growth factors like vascular endothelial growth factor (VEGF); and proteases Pai1, MMP9, and MMP13.[64] The SASP is largely a transcriptional response to common senescence inducers (e.g., telomeric attrition, genomic instability, oxidative stress, oncogenic stress to lead to tumor activation, and mitochondrial dysfunction) mediated in part by the pro-inflammatory transcription factor nuclear factor κB (NF-κB) and the cyclic GMP-AMP synthase and the stimulator of interferon genes (cGAS-STING) pathway.[56,65] SASP can also be regulated post-transcriptionally; for example, the mechanistic target of rapamycin (mTOR) promotes translation of IL-1α to activate NF-κB.[66] The SASP can act in a paracrine manner, inducing senescence of surrounding cells.[62,67] The SASP is a contributing factor to the chronic inflammation seen during aging, obesity, and metabolic dysfunction.[63,64,68]

The inducer of senescence can affect the SASP produced as well as affect the number of alterations in SASP.[69] For example, mitochondrial dysfunction-associated senescence (MiDAS) has a distinct SASP, one that is independent of NF-κB signaling, leading to a lack of IL-1 and IL-6 signaling.[70] Senescence induced by oncogenic RAS produces an amplified SASP.[62] Damage-associated molecular patterns (DAMPs) representative marker HMGB1 mediates SASP in a p53-dependent manner and is independent of p16.[71] This suggests that the SASP produced will be dependent on the inducer, and determining what SASP to assess should be thought through on a case-by-case basis. This also suggests that the SnC markers themselves may have their own respective SASP. In line with this, the SASP produced by SnCs between tissues and likely cell types also varies, as significant differences in the SASP between $p16^{INK4a}$ and $p21^{CIP1}$ positive SnCs in different tissues have been observed, with $p21^{CIP1}$ positive SnCs being more inflammatory and expressing more SASP factors.[72,73]

Morphological alterations

SnCs are enlarged and irregularly shaped,[74] with changes in nuclear morphology.[75] Alterations in the unfolded protein response contribute to the increase in cell size in SnCs.[76] Lamin B1 is a crucial protein that maintains nuclear structure and is downregulated in SnCs,[58] and the loss of lamin B1 can lead to the release of cytoplasmic chromatin fragments into the cytoplasm, the activation of cGAS-STING, and the production of SASP factors.[77,78] Senescence is also characterized by an upregulation of lysosomal proteins and increased lysosomal content.[56] One of the most widely used markers of senescence is increased levels of senescence-associated β-galactosidase (SA-β-Gal),[79] a lysosomal hydrolase enzyme encoded by *Glb1* that catalyzes the hydrolysis of β-galactosides. SA-β-Gal expression increases with senescence and aging.[59,80–83] Conversely, knockdown of the *Glb1* gene is associated with improved health and reduced senescence.[84] Interestingly, while SnCs have altered intercellular pH due to the altered lysosomal content, this change is followed by increased glutaminolysis to neutralize the drop on intracellular pH.[85]

Senescence can alter tissue architecture in the surrounding space. SnCs alter the extracellular matrix (EMC) by affecting ECM degradation, ECM formation, and ECM tensioning as well as affecting tissue fibrosis.[86,87] Additionally, many morphology-based machine learning and modeling technologies have become available to assess senescence within tissue, such as the senescence-associated morphological profiles (SAMPs), which take many factors, including cell size, nuclear size, nuclear shape, etc, into account to determine if a cell is senescent[88]; the fully automated senescence test (FAST), which is an image-based method for a high-throughput, single-cell assessment of senescence in cultured cells[89]; an algorithm to assess for senescence based on nuclear size[90]; the cascade region-based convolution neural network, called cascade R-CNN[91]; and the detector of mitosis, apoptosis, interphase, necrosis, and senescence (D-MAINS) can be used for phase contrast images[92] and the cancer-based transfer learning and ensemble learning method in nonlinear optical microscopy images.[93]

Signatures of senescence

Several senescence/SASP gene sets for identifying SnCs have been recently developed, including SenMayo and SenSig, which identify SnCs across tissues and species with high fidelity.[94,95] These SnC gene sets utilize single-cell RNA sequencing to understand changes within the cell, but they can also uncover signaling crosstalk between SnCs and other cell types. These gene sets can potentially serve as a clinical panel for monitoring SnC with aging and identifying new drugs to clear SnCs. SenMayo includes changes in factors related to metabolism, such as many of the insulin-like growth factor (IGF)-binding proteins, which are important growth factors.[94] This is important as SnCs display many metabolic alterations, many of which are utilized to promote cell survival.[96] Many metabolites related to energy balance, redox homeostasis, and antioxidants have been shown to be altered within a SnC.[97] For example, SnCs adopt a more glycolytic state, which is regulated by pyruvate metabolism as well as reduce malate metabolism, leading to a decreased nicotinamide adenine dinucleotide (NAD^+)/NADH state and decreased cell proliferation.[96] Additionally, a new machine learning program senescent cell identification (SenCID) method utilizes bulk and single-cell transcriptome can identify 6 different type of SnCs with different trajectories and susceptibilities to senolytics.[98] These gene sets are in addition to the following gene sets linked to senescence: SeneQuest,[8] CellAge,[99] CSGene,[100] the conserved gene expression signature of mammalian aging,[101] the GO term cellular senescence,[102] the KEGG pathway cellular senescence,[103] and the reactome pathways of cellular senescence and SASP.[104] Many of these senescence gene sets have been reviewed[105] and analyzed to determine a ubiquitous gene set; see the following preprint by Qu and Ji.[106]

Limitations of methodologies

The emergence of many new technologies for assessing senescence could not have come at a better time because there have

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been many weaknesses in senescence and SASP assessment methodologies. First, there is also a lack of universal biomarkers, as commonly used senescence markers such as *p16* and *p21* are differentially expressed depending on the tissue, and the SASP produced by these *p16*-positive and *p21*-positive cells varies depending on the inducer.[69,70,72,73] As an immunohistochemical method to visually assess senescence, SA-β-Gal is widely used to identify senescence, but it does have limitations. Specifically, it can only be used on fresh tissue, and its sample preparation is potentially incompatible with other fixation and sample preparation methods.[58,79] SA-β-Gal staining also may not be fully specific for senescence as apoptotic non-SnCs in developing limbs and healthy neurons during early embryonic development can also stain positively for SA-β-Gal[107] as well as can be affected by cell density *in vitro*.[108] Additionally, due to the lack of universal markers and the heterogeneity of SnCs, there provides a challenge to mapping SnCs within the tissue. Single-cell methodologies have advanced significantly to allow for the characterization of SnC but still do not provide sufficient spatial insights, which is important since SnCs communicate with nearby cells to affect their function and composition of their extracellular space.[86] For a full review on the current methodologies for visually assessing senescence, see Gurkar et al.[86]

Metabolic dysfunction

The accumulation of SnCs is linked to a decline of organ metabolism, ultimately resulting in age-related and metabolic diseases, such as obesity and type-2 diabetes (T2D).[4,5,64,109–116] Both obesity and T2D can lead to the progression of other age-related diseases such as cardiovascular disease, kidney disease, and cancer,[117–120] putting individuals with these diseases at risk for early mortality.

Senescence in multiple tissues has been associated with metabolic dysfunction. β-cell senescence leads to a worsening metabolic profile, becoming a risk for T2D.[46] Additionally, human subcutaneous fat from very obese individuals displayed increased SnC burden and is associated with increased insulin resistance,[121] a pathophysiological aspect of T2D. Another disease characterized by organ dysfunction is non-alcoholic fatty liver disease (NAFLD), which affects approximately 30% of the Western world.[122] SnCs in the liver have been shown to drive hepatic steatosis, a progression past NAFLD.[123,124] By contrast, clearance of SnCs results in improvements in these metabolic disorders such as T2D or NAFLD.[46,53,116,125,126]

CR AND CELLULAR SENESCENCE

CR, the gold standard diet for aging interventions, slows multiple hallmarks of aging, including senescence.[55,127] CR reduces SnC burden, as assessed via SA-β-gal, p16, p21, DNA damage (γH2AX), and DNA repair (BRG1) in the liver, white adipose tissue (WAT), pancreas, and kidneys in as little as 8 weeks.[123,128–136] This effect is conserved in other organisms, including rats, where CR reduces SA-β-gal activity and expression of $p16^{INK4a}$ and $p21^{CIP1}$ in the kidneys and cardiomyocytes.[130,137,138] Treatment of human diploid fibroblasts with serum from CR-fed Fisher-344 rats decreases SA-β-gal activity.[129]

In humans, 10 years on 30% CR decreased expression of *p16*, *IL-6*, *IL1α*, and *Mmp9* in the sigmoidal colon mucosa,[139] while a 12–24 month intervention significantly reduced the expression of the SenMayo gene set in WAT.[140] CR for 18 weeks decreases circulating senescence biomarkers in aged individuals[141] and in the WAT of overweight/obese women when combined with resistance training.[142] The CALERIE-II clinical trial in which humans underwent 2 years of a 14% CR regimen found a decrease in two matricellular proteins: secreted protein acidic and rich in cysteine (SPARC) and platelet activating factor acetyl hydrolase (PLA2G7), both of which led to protection against inflammation and metabolic dysregulation in mice,[143,144] suggesting CR may potentially protect against WAT senescence in humans. A full list of how CR affects senescence is shown in Table 1.

DIETARY MACRONUTRIENTS AND CELLULAR SENESCENCE

While CR has historically been viewed as a difficult intervention to adhere to, it is a highly effective dietary intervention. A potential dietary alternative in humans may be to reduce the consumption of dietary macronutrients (i.e., protein, carbohydrates, and fats) to mediate similar benefits to CR. Whereas the ability of dietary interventions to extend lifespan is well documented, how dietary macronutrients impact senescence is less clear.

Protein

Despite prevailing dietary advice, higher protein consumption is associated with increased rates of cancer, diabetes, and diabetes mortality.[54] Protein restriction (PR) promotes metabolic health in both humans and rodents and extends healthspan and lifespan in mice.[146–152] While there have been only a few studies examining how protein effects senescence, a recent study found that expression of *p16* and *p21* in the liver is associated with protein consumption,[153] and PR reduces *IL1α* and *TNFα* in the livers of old male mice.[154] A list of studies showing how dietary protein affects senescence is found in Table 2.

Amino acids

These results of PR suggest that individual amino acids may affect SnC burden. For example, 82.5% methionine restriction (MR), which extends lifespan in rodents,[164–168] decreases p16, p21, and SASP in C57 male kidneys.[156] Additionally, a 97% MR decreases SA-β-Gal expression in cultured human diploid fibroblasts,[157] as well as decreases p16 and p21 and increases lamin B1 expression in human cardiac fibroblasts.[169] Interestingly, a 5-week intervention of a methionine-choline-deficient (MCD) diet increases liver injury and NAFLD score, which pairs with increased inflammation,[170] suggesting an increase in senescence.

Many of the benefits of PR are the result of reduced levels of the dietary branched-chain amino acids (BCAAs; leucine, valine, and isoleucine). BCAA restriction (BCAA-R) improves the metabolic health of C57BL/6J mice and has male-specific benefits on frailty and lifespan,[149,152,171] Restriction of isoleucine alone not only extends lifespan but also reduces expression of *IL1α* in the liver of HET3 mice after 18 months of intervention begun at 6 months of age.[159] By contrast, restricting isoleucine starting late in life leads to increased expression of *p21* in the liver of male mice.[155] Conversely, depletion of amino acid transporter SLC6A15 or overexpression of BCAT1, an enzyme that mediates

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Table 1. Calorie restriction and its effect on senescence

% Restriction	Senescence marker	SASP marker	Species and sex	Start age and duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
40%	decreased p21, γH2AX	decreased TNF-α, IL-6, and CCL2	C57BL/6 mice (male)	1 year old mice for 28 weeks	epididymal WAT	N/A	Yan et al.[134]
40%	decreased p16	N/A	Fischer-334 rats (male and female)	28 months of age upon sacrifice	adrenal, heart, kidney, ovary, and testis	N/A	Krishnamurthy et al.[133]
40%	decreased SA-β-Gal and p16	N/A	Fischer-334 rats (male and female)	28 months of age upon sacrifice	kidney	N/A	Krishnamurthy et al.[133]
20%	decreased *p16* and *p21*	N/A	C57BL/6 mice (male)	8-week-old mice for 12 months	pancreas	suppression of mTORC1	Dos Santos et al.[135]
40%	decreased SA-β-Gal	N/A	C57BL/6 mice (male and female)	25–26 months of age upon sacrifice	kidney	likely not growth hormone	Krishnamurthy et al.[133]
10%–40%	N/A	decreased mmp9	C57BL/6 mouse (male)	20 weeks of age for 12 weeks	proximal colon	N/A	Fontana et al.[139]
10%–40%	decreased p16 and p21	decreased IL-1α, Mmp9, and Cxcl1	C57BL/6 mouse (male)	20 weeks of age for 12 weeks	medial colon	N/A	Fontana et al.[139]
10%–40%	decreased p21	decreased IL-1α, Mmp9, and Cxcl1	C57BL/6 mouse (male)	20 weeks of age for 12 weeks	distal colon	N/A	Fontana et al.[139]
30%	decreased p16	decreased IL-6, IL-1α, and Mmp9	human (sex N/A)	61.7 ± 8.4 years for an average of 10.1 years	human sigmoidal colon mucosa	N/A	Fontana et al.[139]
26%	decreased γH2AX	N/A	mouse C57BL/6 (sex N/A)	13–15.4 months of age for 3 months	hepatocytes	reduced ROS	Wang et al.[132]
26%	reduced SA-β-Gal	N/A	C57BL/6 mouse (sex N/A)	13–15.4 months of age for 3 months	intestinal crypt enterocytes	reduced ROS	Wang et al.[132]
40%	decreased gH2AX, senescence-associated distension of satellites, karyomegaly	N/A	C57BL/6 mouse (male)	3 months of age until 15 months	hepatocytes	N/A	Ogrodnik et al.[123]
26%	decreased γH2AX and p21	decreased IL-6	C57BL/6J mice (male)	15 months of age for 2.5 months	gonadal adipose tissue	N/A	Ishaq et al.[128]
28%	decreased γH2AX, phospho-p38, and SA-β-Gal	N/A	C57BL/6J mice (male)	14 months of age for 3 months	post-mitotic cells (Purkinje cells)	reduced ROS	Jurk et al.[131]
Unknown (alternate day fasting and feeding)	increased BRG1	N/A	BALB/c albino mice (female)	18 months of age for 3 months	liver	N/A	Swer et al.[136]

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Table 1. ***Continued***

% Restriction	Senescence marker	SASP marker	Species and sex	Start age and duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
60%	decreased C12FDG (galactosidase substrate)	N/A	C57BL/6J mice (male and female)	unknown length of time 22 months of age	subcutaneous WAT stem cells	Increased autophagy, suggesting decreased mTOR	Chinnapaka et al.[145]
40%	decreased SA-β-gal	N/A	Sprague-Dawley rats (male)	25 months of age for 8 weeks	kidney	increased Sirt1 and AMPK decreased mTOR	Ning et al.[130]
40%	decreased p16, p21, and SA-β-Gal	N/A	Sprague-Dawley rats (male)	3-month- and 25-month-old male rats for 8 weeks	kidney	increased AMPK decreased mTOR	Dong et al.[137]
40%	decreased SA-β-gal and p53	N/A	human (sex N/A)	sera from male Fisher-344 rats for 6 months given to cells	IMR-90 cells	increased SIRT1	de Cabo et al.[129]
40%	reduced cardiomyocyte size and SA-β-gal	N/A	Fischer-344 rats (male)	7-month-old	cardiomyocyte	decreased mTOR	Shinmura et al.[138]
30%	decreased SenMayo gene set	N/A	human (male and female)	average 37–38 years old for 12–24 months	adipose tissue	N/A	Aversa et al.[140]
30%	N/A	decreased IL-7, VEGF, Pai1, PARC, MMP1, MPO, TARC, TNFR1, and RANTES	human (male and female)	average 37–38 years old for 12 months	plasma	N/A	Aversa et al.[140]
30%	N/A	decreased Pai1, PARC, TARC, ICAM1, TNFR2, and TNFR1	human (male and female)	average 37–38 years old for 12 months	plasma	N/A	Aversa et al.[140]
10%	N/A	decreased activin A, Fas, sICAM-1, MMP1, PAI-1, TNFRI, TNFRII, TNF-α, uPAR, and VEGF	human (male and female)	average 57.6 ± 5.8 years old for 18 weeks	plasma	N/A	Justice et al.[141]
−600 kcal/day combined with resistance exercise	decreased p16	N/A	human (female)	average 72.9 ± 3.4 years old for 5 months	adipose tissue near the vastus lateralis	N/A	Justice et al.[142]

CR protects against senescence in multiple tissues of mice, rats, and humans. IMR-90 cells are human diploid fibroblasts.

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Table 2. Altered dietary protein and amino acids and their effect on senescence

Diet change	Senescence marker	SASP marker	Species and sex	Start age and duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
10%–30% protein in diet (baseline is 20%)	increased *p16* and *p21*	increased *IL6*, *IL1α*, *IL1β*, *TNFα*, *Cxcl1*, *Ccl2*, and *Pai1*	C57BL/6 males	12 weeks old for 12 weeks	liver	N/A	Nehme et al.[153]
67% PR	N/A	reduced IL1α and TNF-α	C57BL/6 mouse (males)	20 months to 24 months	liver	reduced mTOR	Yeh et al.[155]
82.5% Restriction of methionine	decreased p16, p21, and p53	decreased IL-1β, reduced circulating IL-1β, and trended IL-6	C57BL/6 mice (males)	20 months to 22 months	kidney	increased AMPK	Wang et al.[156]
97% Methionine restriction in DMEM	decreased SA-β-Gal	N/A	human (sex N/A)	N/A	diploid fibroblasts	N/A	Kozieł et al.[157]
97% Methionine restriction in DMEM	decreased p21, p16, and lamin B1	N/A	human (sex N/A)	N/A	cardiac fibroblasts	N/A	Kozieł et al.[157]
3% kcal increase coming from BCAAs	N/A	increased Tnf and Mcp1	C57BL/6 mice (males)	4 months to 12 months	inguinal WAT	N/A	Mu et al.[158]
3% kcal increase coming from BCAAs	N/A	increased, Inf-γ, Mcp1, Tnf, and Cxcl5	C57BL/6 mice (males)	4 months to 12 months	epididymal WAT	N/A	Mu et al.[158]
3% kcal increase coming from BCAAs	N/A	increased Inf-γ, Mcp1, and Tnf	C57BL/6 mice (males)	4 months to 12 months	liver	N/A	Mu et al.[158]
67% Isoleucine restriction	N/A	reduced IL1α	UM-HET3 mice (males)	6 months to 24 months	liver	increased FGF21	Green et al.[159]
67% Isoleucine restriction	increased p21	N/A	C57BL/6 mice (males)	20 months to 24 months	liver	N/A	Yeh et al.[155]
1,000 mg/kg BW/day supplementation taurine	decreased SA-β-Gal	N/A	C57BL/6 mice (female and male)	14 months to 24 months	liver, fat, brain, muscle, gut	N/A	Singh et al.[160]
20 mM taurine supplementation in alpha MEM	decreased SA-β-Gal	N/A	C57BL/6 mice (sex N/A)	7 days	primary osteoblasts	N/A	Singh et al.[160]
300 μM and 10 mM taurine supplementation	decreased SA-β-Gal	N/A	Tert−/− zebrafish (sex N/A)	2 to 10 days post-fertilization	whole embryo body	N/A	Singh et al.[160]
1 mM L-arginine supplementation	decreased SA-β-Gal	N/A	human (sex N/A)	72 h	HUVEC	N/A	Hayashi et al.[161]
0.5 mmol/L L-arginine in RPMI-1640 (from 0.1 mmol/L)	increased SA-β-Gal	N/A	human (sex N/A)	7 days	HUVEC	increased mTORC1	Xiong et al.[162]
4 mM proline supplementation	decreased γH2AX, SA-β-Gal, p53, and p21	decreased IL-1α, IL-1β, and il8	human (sex N/A)	14 days	mesenchymal stem cells	increased AMPK decreased ROS	Choudhury et al.[163]

Dietary protein and specific amino acids promote senescence. DMEM is Dulbecco's modified eagle medium. HUVEC cells are human umbilical vein endothelial cells. RPMI is Roswell Park Memorial Institute medium. Alpha MEM is a modified Eagle medium designed for growth.

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Please cite this article in press as: Calubag et al., A nutrigeroscience approach: Dietary macronutrients and cellular senescence, Cell Metabolism (2024), https://doi.org/10.1016/j.cmet.2024.07.025

the catabolism of BCAAs, both lead to decreased intracellular BCAAs and significant attenuation of the SASP in mouse liver and fibroblast culture.[172] Similarly, inhibition of the age-related increase of miR-743b-3p prevents hepatocyte senescence via the regulation of BCAA catabolism.[173] In human HepG2 hepatocellular carcinoma cells, BCAA supplementation enhances premature senescence.[174] An approximately 57% increase in the dietary levels of BCAAs for 12 months resulted in increased *Mcp1* and *Tnfα* expression in the liver, inguinal WAT, and epididymal WAT, which may be SASP-driven.[158]

Several non-essential amino acids may also play a role in regulating senescence. Taurine declines with age in several species, and dietary supplementation with taurine extends mouse lifespan.[160] Intriguingly, taurine supplementation reduces senescence in mouse osteoblast culture, mice, and zebrafish.[160] Supplementation of proline, which, like taurine, declines with age, reduces senescence in cultured mesenchymal stem cells (MSCs).[163] Supplementation with arginine decreases SA-β-Gal expression in cultured cells.[161] However, this may only be a short-term benefit as long-term exposure to arginine accelerates senescence.[162] Studies showing how amino acids affect senescence are listed in Table 2.

Although at least 7 amino acids seem to impact senescence, there are also 13 other common dietary amino acids and additional rare dietary amino acids that have yet to be assessed for effects on senescence. Therefore, we still do not fully understand how individual amino acids impact SnC burden. Additionally, it is unclear if proteins from different dietary sources may impact senescence differently. For example, protein sourced from plants rather than animals has been associated with a lower risk of metabolic syndrome,[175] suggesting that protein source could also have an affect SnC burden.

Carbohydrates

The next dietary macronutrient we will discuss is carbohydrates. Culturing various types of cells in high glucose media accelerates senescence, including human retinal endothelial cells, human skin fibroblasts, renal tubular epithelial cells, bovine retinal endothelial cells, and human diploid fibroblasts.[176–180] By contrast, restricting glucose in the media extends their replicative lifespan and decreases senescence in endothelial cells and IMR-90 human diploid fibroblasts.[161,176,181]

In addition to glucose, sugar sources have been shown to impact organ function and senescence accumulation. For example, fructose leads to fatty liver and/or liver cancer.[182–185] It may also drive anti-tumor activity in adipocytes.[186] A high sucrose Western diet (WD) supplemented with glucose and fructose in the water increases senescence in the liver of mice.[187] A high-fat, high-fructose diet induces senescence in the hippocampus of mice.[188] In cultured fibroblasts, fructose supplementation induces SASP production.[189]

Culturing primary human fibroblasts in galactose as well as silencing galactokinase, the enzyme that breaks down galactose, accelerates senescence.[190] D-galactose induces senescence in glioblastoma cell lines.[191] In mice, D-galactose injections accelerate the aging phenotype in the brain and liver.[192–194] Administration of D-galactose leads to significant inflammation across many tissues (reviewed in Azman and Zakaria[195]), suggesting that in mammals, D-galactose in the diet can induce senescence *in vivo*, leading to this increase in inflammation. This potent effect on inflammation may be mediated by the induction of mTOR complex 1 (mTORC1; see below), which has been shown to be induced by galactose in MSCs and rodent skin.[196–198] Studies showing how carbohydrates affect senescence are listed in Table 3.

Although glucose, fructose, and galactose can induce senescence, there is limited evidence that high-fructose corn syrup (HFCS) impacts the SnC burden. HFCS is a highly refined sugar that makes up 40% of sweetener in the United States and plays a role in liver pathologies, such as hepatic steatosis,[204] which is associated with SnC burden and poorer metabolic outcomes. Additionally, while a WD in combination with HFCS in the water induces senescence,[205] it is unclear if HFCS can induce senescence alone since a WD induces senescence even without HFCS (Table 4). Importantly, carbohydrates include simple sugars and complex carbohydrates, and this review mainly focused on simple sugars. Resistant starches, a type of complex carbohydrate, are suspected to mitigate age-related inflammation,[206] suggesting there could be an effect on senescence. Consistent with this, mice fed a diet with more resistant starches have reduced senescence and SASP gene expression in various tissues (Table 3).[203] Overall, it seems that while simple sugars induce senescence, complex carbohydrates in the form of resistant starches may protect against it.

Fats

High-fat (60%) and/or high-fat (40%), high sucrose WDs (HFD and WD, respectively) have been shown to negatively impact metabolic health and lifespan.[223,224] Approximately 70% of Americans are overweight or obese, leading to an increased risk of developing age-related diseases.[225] Specifically, HFD and WD can lead to diabetes, obesity, and cardiovascular disease.[224,226] These negative consequences of HFD and WD may be due, in part, to the accumulation of SnCs in response to the diet.

In multiple mouse strains, a HFD induces senescence in the epididymal WAT (eWAT) in as little as 2 months.[47,123,212–214,216] It also increases the SnC burden in the amygdala, hippocampus, cortex, kidney, liver, skin, bone marrow-derived MSCs, and aorta of various mouse strains.[207–209,211,216,217,219] In addition, there is increased expression of senescence markers in the gonadal WAT, subcutaneous WAT, and liver of the $p16^{INK4a}$-eGFP mouse strain on a genetically heterogeneous background in response to WD.[205]

This accumulation of SnCs in these tissues is associated with varying diseases or impairments in quality of life. For example, hepatocyte senescence caused by a HFD is associated with NAFLD,[123] increasing the risk of all-cause mortality as well as mortality due to cardiovascular events and hepatocellular carcinoma.[122,227] Senescence in the aorta, which has the highest SnC burden in aged mice,[228] causes susceptibility to ischemic injury, which has the potential to cause chronic tissue damage and dysfunction.[211] Consistently, ischemic injury-induced cardiac senescence impairs heart function and causes improper remodeling following the cardiac ischemia-reperfusion.[229,230] HFD-induced senescence in the amygdala can lead to increased anxiety and decreased neurogenesis.[207] Additionally, stroke-induced senescence in the brain releases SASP, which can cause loss of neurological function.[231]

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Table 3. Altered dietary carbohydrates and their effect on senescence

Diet change	Senescence marker	SASP marker	Species and sex	Start age and duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
22 mM D-glucose in Eagle's minimal essential medium (increase from 5.5)	increased SA-β-Gal	N/A	human males	after 35 to 50 population doublings	foreskin fibroblasts	N/A	Blazer et al.[179]
25 mM D-glucose in endothelial cell medium (increase from 5)	increased SA-β-Gal and cell size	N/A	human (sex N/A)	4 weeks	retinal microvascular endothelial cells	N/A	Bertelli et al.[180]
25 mM D-glucose in Click's medium/RPM1-1640 (increase from 8)	increased SA-β-Gal and p21	N/A	Caucasian non-hypertensive human (sex N/A)	3 day intervention	proximal tubular cells	N/A	Kitada et al.[178]
25 mM D-glucose in DMEM (increase from 3.3 and 5.6)	increased SA-β-Gal and p16	N/A	human (sex N/A)	after 20 population doublings	WI-38 cells	N/A	Zhang et al.[177]
25 mM D-glucose in DMEM (increase from 2.2 or 3.3)	increased SA-β-Gal	N/A	human (sex N/A)	26–35 population doublings	IMR-90 cells	N/A	Jin and Zhang et al.[181]
22 mM D-glucose in DMEM (increase from 5.5)	increased SA-β-Gal	N/A	human (sex N/A)	72 h	HUVEC cells	N/A	Hayashi et al.[161]
11 and 22.0 mM glucose in DMEM (increase from 0)	increased SA-β-Gal, p16, p53, and p21	N/A	Sprague-Dawley rat (male and female)	14 days	mesenchymal stem cells	increased mTOR	Zhang et al.[199]
25 mM glucose in media (increase from 5.5)	increased p16	N/A	human (sex N/A)	25 and 48 population doublings	HUVEC cells	increased phosphorylation of Akt, suggesting increased mTOR	Rogers et al.[200]
27 mM D-glucose in DMEM (increase from 4.5)	increased SA-β-Gal, p21, and p16	N/A	mouse (sex N/A)	48 h	HT22 cell	N/A	Wu et al.[201]
Water containing 23.1 g/L D-glucose and 18.9 g/L D-fructose and a Western diet with 405.36 g of sucrose/kg	increased p21 and SEN_MAYO dataset	N/A	C57BL/6 mice (sex N/A)	2.5 month old for 26 weeks	liver	N/A	Massemin et al.[187]
1 g/L fructose in DMEM	N/A	increased IL-1α, IL-6, IL-8, MCP1, and TNF1α	C57BL/6 mice (males)	N/A	interscapular brown fat pads	N/A	Elsaid et al.[189]
20% fructose supplementation in the water with a high-fat diet	increased SA-β-Gal, p53, p21, and p16	N/A	C57BL/6 mice (females)	9 week old for 12 weeks	hippocampus	N/A	Jang et al.[188]
10% lard and 30% fructose supplementation	increased p21 and SA-β-Gal	N/A	BALB/c mice (male)	4–6 weeks of age for 4 months	liver	N/A	Qin et al.[202]
10 mM galactose in glucose-free DMEM	increased SA-β-Gal	N/A	human (sex N/A)	48 h	IMR-90 cells	N/A	Elzi et al.[190]
55, 111, and 222 mM D-galactose in DMEM/nutrient mixture F-12	increased SA-β-Gal	N/A	rat (sex N/A)	8 days	C6 cells	N/A	Xu et al.[191]

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Table 3. *Continued*

Diet change	Senescence marker	SASP marker	Species and sex	Start age and duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
222 mM D-galactose in DMEM/ nutrient mixture F-12	increased p53, p16 decreased lamin B1	increased NF-kB	rat (sex N/A)	8 days	C6 cells	N/A	Xu et al.[191]
222 mM D-galactose in DMEM/ nutrient mixture F-12	increased SA-β-Gal, p53 decreased lamin B1	N/A	human (male)	7 and 9 days	U87MG cells	N/A	Xu et al.[191]
40% fat with 0.2% cholesterol; Western diet with 5% pinto bean resistant starches	decreased *p16*	decreased *IL10* and *IFNγ*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	hypothalamus	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% black-eyed pea resistant starches	decreased *p16* and *p21*	decreased *IFNγ* and *IL1β*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	hypothalamus	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% lentil resistant starches	decreased *p16* and *p21*	decreased *IL8* and *IFNγ*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	hypothalamus	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% chickpea resistant starches	decreased *p21*	N/A	C57BL/6 mice (males)	60-week-old mice for 20 weeks	hypothalamus	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% chickpea resistant starches	decreased *p21*	N/A	C57BL/6 mice (males)	60-week-old mice for 20 weeks	colon	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% lentil resistant starches	decreased *p16* increased *p21*	N/A	C57BL/6 mice (males)	60-week-old mice for 20 weeks	ileum	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% black-eyed pea resistant starches	increased *p21*	N/A	C57BL/6 mice (males)	60-week-old mice for 20 weeks	ileum	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% pinto bean resistant starches	decreased *p16*	N/A	C57BL/6 mice (males)	60-week-old mice for 20 weeks	ileum	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% pinto bean resistant starches	N/A	decreased *IL6*, *IL8*, and *IL10*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	frontal cortex	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% lentils resistant starches	N/A	decreased *IL8*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	frontal cortex	N/A	Kadyan et al.[203]
40% fat with 0.2% cholesterol; Western diet with 5% chickpea resistant starches	N/A	decreased *IL8* and *IL10*	C57BL/6 mice (males)	60-week-old mice for 20 weeks	frontal cortex	N/A	Kadyan et al.[203]

Simple sugars, such as glucose, fructose, and galactose, promote senescence in culture and mice. Complex starches may be able to protect against senescence. HUVEC cells are human umbilical vein endothelial cells. WI-38 and IMR-90 cells are fibroblast cell lines. C6 and U87MG are glioma cell lines. HT22 cell line is a mouse hippocampal neuron cell line.

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Table 4. Altered dietary fats and its effect on senescence

Diet change	Senescence marker	SASP marker	Species and sex	Start age and Duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
60% fat (lard)	increased SA-β-Gal, p16, p21, and γH2AX	increased G-CSF, IL1α, IL1β, Cxcl1, Mcp1, Mig, and Tnf-α	INK-ATTAC$^{+/-}$ mice (sex N/A)	started at 8 months until 13 months	gonadal WAT	N/A	Ogrodnik et al.[207]
60% fat (lard)	increased p16 and γH2AX	N/A	INK-ATTAC$^{+/-}$ mice (sex N/A)	started at 8 months until 13 months	amygdala	N/A	Ogrodnik et al.[207]
60% fat (source not specified)	increased SA-β-Gal and p19	N/A	C57BL/6J mice (sex N/A)	8.5 months	kidney	N/A	Kim et al.[208]
60% fat	increased p16 and SA-β-Gal	increased IL-6, IL-1β, and TNFα	C57BL/6J mice (female)	started at 6 weeks old for 12 weeks	hippocampus and cortex	increased ROS	Hou et al.[209]
High-fat (did not specify percentage)	increased p16	N/A	Sprague-Dawley rats (sex N/A)	start at 3 weeks for 9 weeks	liver	N/A	Zhang et al.[210]
60% fat (lard)	increased SA-β-Gal and p16 and p21	N/A	C57BL/6 J mice (male)	start at 4–16 weeks of age for 12 weeks	aorta and aortic endothelial cells	increased mTOR	Wang et al.[211]
40% fat (milk fat, 12% saturated) with 0.2% cholesterol; Western diet	increased p16, p53, p21, and SA-β-Gal	increased IL-6, Pai1, MCP1, and MMP3	p16^{INK4a}-eGFP heterogeneous mice (sex N/A)	8-month-old male mice for 4 months	epididymal WAT	N/A	Schafer et al.[205]
40% fat (milk fat, 12% saturated) with 0.2% cholesterol; Western diet	increased p21	N/A	p16^{INK4a}-EGFP heterogeneous mice (sex N/A)	8-month-old male mice for 4 months	subcutaneous WAT	N/A	Schafer et al.[205]
40% fat (milk fat, 12% saturated) with 0.2% cholesterol; Western diet	increased p21	N/A	p16^{INK4a}-EGFP heterogeneous mice (sex N/A)	8-month-old male mice for 4 months	liver	N/A	Schafer et al.[205]
60% fat (lard)	increased p16, p21, and SA-β-Gal	N/A	C57BL/6J mice (male)	5-month-old on diet for 10 weeks	epididymal WAT	increased ATP, suggesting inhibition of AMPK	Pini et al.[212]
60% fat (lard)	increased p16, p21, and SA-β-Gal	N/A	C57BL/6J mice (male)	5-month-old on diet for 10 weeks	inguinal WAT	increased ATP, suggesting inhibition of AMPK	Pini et al.[212]
60% fat (lard)	increased p21	N/A	C57BL/6J mice (male)	2-month-old for 2 months	gonadal WAT	N/A	Wang et al.[213]
60% fat (lard)	increased p21 and p16	N/A	C57BL/6J mice (male)	2-month-old for 10 months	gonadal WAT	N/A	Wang et al.[213]
60% fat (lard)	increased SA-β-Gal and γH2AX	N/A	C57BL/6 mice (sex N/A)	start 4 weeks old until 18 weeks old	epididymal WAT	N/A	Shirakawa et al.[214]
N/A	increased SA-β-Gal and p53	increased VEGF and Mmp9	fattening *Wagyu* steers (male)	N/A	epididymal WAT	N/A	Yamada et al.[215]

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Table 4. *Continued*

Diet change	Senescence marker	SASP marker	Species and sex	Start age and Duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
60% fat (lard)	increased p53 and p16	N/A	C57BL/6 mice (male)	3 weeks of age for 10 weeks	bone marrow	N/A	Alessio et al.[216]
60% fat (lard)	increased p21 and p16	N/A	C57BL/6 mice (male)	3 weeks of age for 10 weeks	subcutaneous WAT	N/A	Alessio et al.[216]
60% fat (lard)	increased p21, p16, and pRb	N/A	C57BL/6 mice (male)	3 weeks of age for 10 weeks	epididymal WAT	N/A	Alessio et al.[216]
N/A	increased SA-β-Gal	increased Pai1, CCl2, and IL6	obese humans (sex N/A)	N/A	subcutaneous WAT	N/A	Rouault et al.[121]
60% fat (lard)	increased SA-β-Gal and p16	N/A	p16-3MR mice (male)	Not disclosed	epididymal WAT	N/A	Palmer et al.[47]
60% fat (lard)	increased p21, p16, and γH2AX	increased IL-6, CXCL9, and IL1β	C57BL/6 mice (males)	30 weeks	liver	N/A	Yoshimoto et al.[217]
60% fat (lard)	increased p16, karyomegaly	N/A	C57BL/6$^{(INK-ATTAC)}$ mice (males)	6 months to 15 months	liver	increased ROS	Ogrodnik et al.[123]
60% fat (not specified) with 20% fructose supplementation in the water	increased SA-β-Gal, p53, p21, and p16	N/A	C57BL/6 mice (females)	9 week old for 12 weeks	hippocampus	N/A	Jang et al.[188]
8.3%–80% fat in diet (baseline is 10%) (source of fat not specified)	N/A	increased IL-6, IL-1α, TNFα, Cxcl10, Pai1, and Ccl2	C57BL/6 mice (males)	12 weeks old for 12 weeks	liver	N/A	Nehme et al.[153]
41% fat with 6.37 mg/g added cholesterol (source of fat not specified)	increased SA-β-Gal	N/A	baboon (sex N/A)	7 weeks	endothelial cells from left and right femoral arteries	N/A	Shi et al.[218]
60% fat (cocoa butter)	increased p16 and p53	increased IL-1β, IL-6, and TNFα	ApoE−/− mice (male)	8 weeks for 12 weeks	skin	N/A	Liang et al.[219]
60% fat (lard)	increased SA-β-Gal	N/A	C57BL/6J mice (male)	13 months old for 24 weeks	hippocampus	decreased AMPK increased mTOR	Chen et al.[220]
10% lard and 30% fructose supplementation	increased p21 and SA-β-Gal	N/A	BALB/c mice (male)	4–6 weeks of age for 4 months	liver	N/A	Qin et al.[202]
60% fat (lard)	N/A	increased TNFα and MCP1	C57BL/6J mice (male)	3 month intervention	epididymal WAT	N/A	Bloom et al.[221]
90.5% kcal from fat (Crisco)	increased SA-β-Gal and γH2aY	N/A	C57BL/6J mice (male)	6 weeks old for 21 days	heart and kidney	increased phosphorylation of AMPK	Wei et al.[222]
90% kcal from fat (cocoa butter)	increased SA-β-Gal and H2aY	N/A	C57BL/6J mice (male)	6 weeks old for 21 days	heart and kidney	N/A	Wei et al.[222]

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Table 4. *Continued*

Diet change	Senescence marker	SASP marker	Species and sex	Start age and Duration	Cell or tissue type	Nutrient pathway (if specified)	Reference
90.5% kcal from fat (Crisco)	increased p53 and p21	increased TNFα, IL-1β, IL-6, and CCL5	C57BL/6J mice (male)	6 weeks old for 21 days	heart and kidney	increased phosphorylation of AMPK	Wei et al.[222]
90.5% kcal from fat (Crisco)	increased p16	N/A	C57BL/6J mice (male)	6 weeks old for 7 days	heart and kidney	increased phosphorylation of AMPK	Wei et al.[222]
90.5% kcal from fat (Crisco)	increased p53, p21, and SA-β-Gal	N/A	C57BL/6J mice (male)	6 weeks old, 24 weeks old, 52 weeks old for 21 days	heart and kidney	increased phosphorylation of AMPK	Wei et al.[222]

Increased dietary fat promotes senescence in multiple tissues of multiple model organisms to humans. Gonadal WAT and epididymal WAT are all names for the white adipose tissue within the peritoneal cavity surrounding the gonads.

Increased expression of senescence markers in response to a HFD is conserved across species in a variety of organs. In Sprague-Dawley rats, a HFD for 9 weeks leads to increased p16 mRNA and protein expression in the liver.[210] Interestingly, fattening Wagyu steers, which are fed a HFD throughout their lives, also display increased SA-β-gal in their inguinal WAT, eWAT, and brown adipose as well as increased p53 in their eWAT.[215] In baboons, a high-fat, high-cholesterol diet increases SA-β-gal activity in the endothelial cells of the femoral arteries.[218] Studies showing how fats affect senescence are listed in Table 4.

It is important to note that many of the high-fat diets used in the studies cited here have lard as the principal fat source, leading to an increase in saturated fatty acids, which promotes senescence. Additionally, SnCs upregulate β-oxidation in oncogene-induced senescence[232] and elevate fatty acid synthesis[233,234] to drive their SASP production, as well as decrease stearoyl-coenzyme A (CoA) desaturase,[235] which breaks down saturated fatty acids, suggesting that saturated fatty acids play a critical role in senescence.[176]

This raises the question of how diets containing primarily unsaturated fatty acids may affect SnC burden and if diets containing larger amounts of saturated fatty acids promote senescence in this way. Free polyunsaturated fatty acids (PUFAs) increase within SnCs[236] where they are incorporated into triglycerides,[237] which can become lipid droplets. Lipid metabolism has been shown to regulate senescence, and the accumulation of triacylglycerols via modification of glycerol-3-phosphate and phosphoethanolamine has been linked to the senescence program in human fibroblasts.[238] Additionally, a low-carbohydrate, high-fat ketogenic diet reduces mid-life mortality and improves healthspan in mice.[239,240] While these studies did not directly examine senescence, intraperitoneal injections of β-hydroxybutyrate, a ketone body produced by ketogenic diets, lowered senescence in mouse muscle and endothelial cells,[241] potentially through the activation of nuclear factor-erythroid-2-related factor 2.[242,243] β-hydroxybutyrate also inhibits the NLRP3 inflammasome in myeloid cells,[244] suggesting it may suppress SASP. However, a recent study showed that a ketogenic diet can induce p53/p21-mediated senescence in multiple organs (Table 4).[222] Given the growing popularity of these diets, research in this area is essential to fully understand these contrasting results between the diet and their metabolites.

MICRONUTRIENTS

An important set of dietary components are micronutrients, consisting of essential vitamins and minerals that play a role in tissue function. Micronutrients also play a role in organismal aging and senescence, particularly with suppression of SASP.[245] Vitamin E has been shown to delay senescence in human umbilical vein endothelial cell (HUVEC) and fibroblast culture.[246] Vitamin D decreases NF-κB activity in murine macrophage cells, suggesting it may reduce SASP.[247] Additionally, expression of a vitamin B_2 transporter reduces senescence in U2OS cells.[248] As mentioned above, an MCD diet increases NAFLD score and inflammation,[170] while MR decreases senescence,[156,157,169] suggesting that choline, a vitamin-like micronutrient, may have health benefits. Outside of vitamins, polyphenols derived from cocoa have

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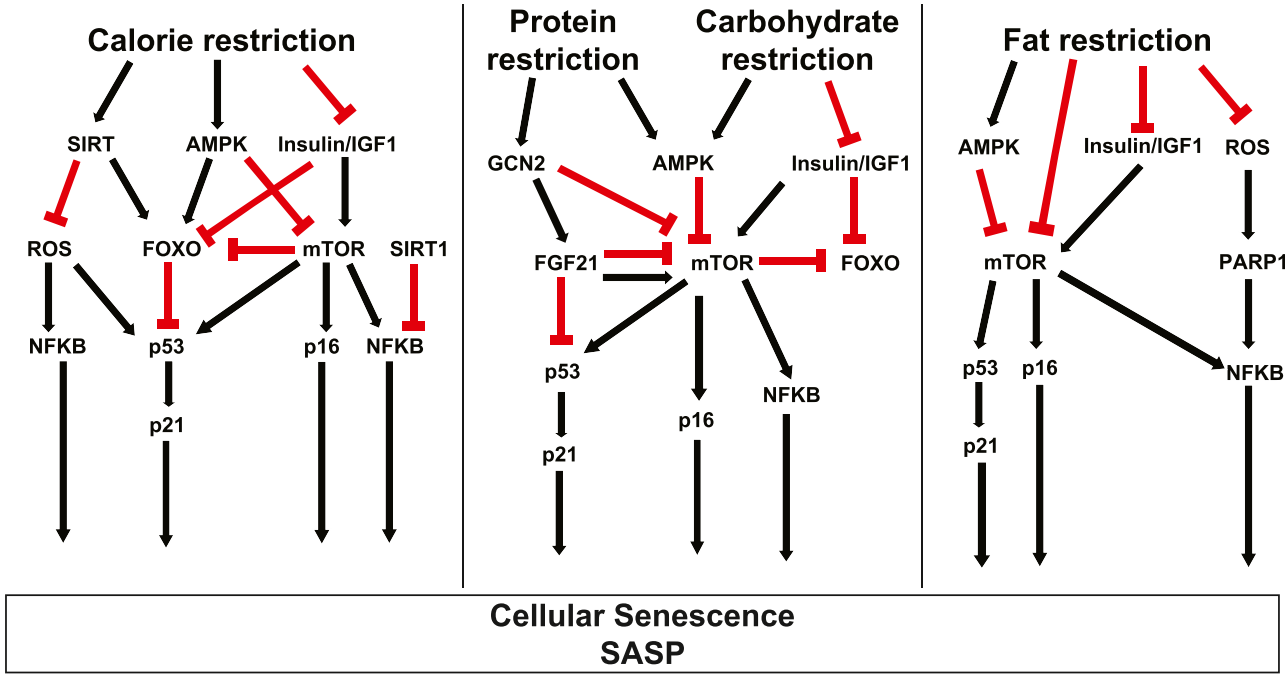


Figure 2. How calorie restriction and restriction of the dietary macronutrients alter nutrient pathways to impact senescence

Calorie restriction engages multiple pathways to reduce senescence. Sirtuins inhibit ROS and NFKB to prevent inflammation, and it promotes FOXO, which inhibits the p53/p21 signaling pathway. AMPK also activates FOXO as well as inhibits mTOR, which promotes the p53/p21 signaling pathway and activates p16 and NFKB, all to promote senescence and SASP. CR has also been shown to decrease IGF1, which acts to promote mTOR and inhibit FOXO to promote senescence. Protein restriction and carbohydrate restriction similarly act to activate AMPK. Carbohydrate restriction also inhibits IGF1. Protein restriction activates GCN2, which in turn can promote mTOR ubiquitination as well as activate FGF21, which can inhibit senescence. FGF21 does have opposing effects on mTOR, promoting it in adipose and inhibiting it in the liver. Fat restriction promotes AMPK signaling and inhibits mTOR and ROS to prevent senescence.

been shown to inhibit senescence via the modulation of sirtuins in auditory cell lines.[249] Procyanidin C1, which is a polyphenolic component of grape seed extract (GSE), reduces SnC burden and increases the healthspan and lifespan of mice.[250,251] In terms of minerals, chronic exposure to high-dose zinc can also accelerate senescence in human endothelial cells.[252] Magnesium deficiency accelerates senescence in cultured cells,[253] while dietary supplementation extends the lifespan of progeroid mice.[254] A polyphenol-rich botanical extract of the plant *Salvia haenkei* has also has been shown to extend health and lifespan as well as reduce senescence in multiple organs.[255] There are still many other micronutrients that have yet to be assessed for their role in senescence. Overall, there is still much we do not know about how dietary micronutrients affect SnC burden and aging.

NUTRIENT-RESPONSIVE PATHWAYS IMPLICATED IN SENESCENCE

There is an intricate network of nutrient-responsive mechanisms by which CR and macronutrient restriction impact cellular senescence. CR activates pro-longevity nutrient sensors such as AMP-activated protein kinase (AMPK), sirtuins, and forkhead box Os (FOXOs) and inhibits negative longevity regulators growth hormone and mTOR, which can reduce the SnC burden.[256,257] For an extensive review on the nutrient-responsive pathways engaged by dietary restriction or different macronutrients, see Green et al.[54] The major nutrient-responsive mechanisms that potentially regulate senescence in the different dietary alterations are summarized in Figure 2.

NAD$^+$ consumers

NAD$^+$ is an essential metabolite that declines with age.[258] SnCs promote this decline of NAD$^+$ during aging.[29] Some of the most well-known NAD$^+$ consumers are the sirtuins, a family of NAD$^+$-dependent protein deacetylases (SIRT1-7) with diverse cellular functions. Sirtuins have been implicated in healthy aging[259] and are strongly activated by CR.[260–264]

There are three nuclear sirtuins: SIRT1, SIRT3, and SIRT7. SIRT1 protects against senescence in many types of cultured human cells,[265–268] which may be due to its role in DNA repair.[269] In mouse embryonic fibroblasts (MEFs), Sir2α and its human homolog SIRT1 antagonize the acetylation of p53 and rescue cells from premature senescence,[270,271] as well as regulate the SASP through modulation of NF-κB. SIRT1 overexpression also protects rat livers from arsenic-induced MiDAS.[272] Conversely, decreased SIRT1 increases senescence in MEFs and other cell types.[266,273–275] SIRT1 may mediate senescence through the regulation of other longevity-related pathways, as reviewed in Ungurianu et al. [276] Overall, SIRT1 has a protective effect against senescence.

SIRT6 is also associated with DNA repair, in particular double-strand break repair.[276,277] SIRT6 overexpression protects against senescence in rat and human nucleus pulposus (NP) cells,[278] while SIRT6 inhibition promotes premature senescence

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in endothelial cells.[279] SIRT6 induces senescence in HUVECs via FOXM1, which promotes superoxide dismutase (SOD) expression,[280] suggesting SIRT6 also may protect against oxidative stress-induced senescence.

There is limited literature on the role of SIRT7 in senescence, but SIRT7 plays a role in cell proliferation and survival,[276,281] and SIRT7 deficiency accelerates senescence in human cells,[282,283] while overexpression of SIRT7 can mitigate senescence in mouse fibroblast culture.[284] However, SIRT7 increases in senescent fibroblasts and aged tissues,[285] and increased SIRT7 expression is correlated with increased SA-β-gal activity in mammary epithelial cells,[286] which could potentially be a compensatory mechanism to counteract the aged or pathogenic tissue.

SIRT2 is a cytoplasmic sirtuin with increased expression observed during senescence.[287] However, other studies suggest SIRT2 may have protective effects against senescence. SIRT2 expression suppresses senescence in human NP cells via the inhibition of the p53/p21 pathway.[288] Additionally, SIRT2 can inactivate the NLRP3 inflammasome in macrophages, and this can prevent NLRP3 inflammasome-dependent age-associated inflammation.[289,290] Downregulated SIRT2 is correlated with increased senescence in the heart of aged primates and in human cardiomyocytes *in vitro*.[291] Clearly, whether SIRT2 has a beneficial or pathogenic role in senescence is still to be determined.

SIRT3-SIRT5 are the mitochondrial sirtuins. In mammary epithelial cells, increased SIRT3 increases with SA-β-Gal expression,[286] suggesting it may play a role in senescence. For example, *Sirt3*-deficient mice on CR have an extended maximum lifespan as compared with the wild-type CR mice, though this was paired with decreased oxidative metabolic capacity, and there was no extension in *Sirt3*-deficient *ad libitum*-fed mice compared with wild-type *ad libitum*-fed mice.[292] Thus, CR-specific lifespan extension in the KOs may be beneficial only in late-life potentially through the reduction in senescence. However, other recent studies suggest that SIRT3 opposes senescence. SIRT3 antagonizes MiDAS in IMR-90 cells as well as counteracts senescence in lung cancer A549 cells, MLE-12 alveolar epithelial cells, mouse lungs, and rat bone marrow MSCs,[70,293–297] likely due to the activation of SOD.[298] Increased SIRT4 promotes reactive oxygen species (ROS) generation[299,300] and is linked to increased SnC burden in human foreskin fibroblasts,[301] suggesting that SIRT4 may promote senescence via oxidative stress. However, in human keratinocytes, overexpression of SIRT4 alleviates oxidative stress-induced senescence.[302] SIRT5 antagonizes MiDAS in IMR-90 cells,[70] while its silencing promotes senescence in umbilical cord blood-derived MSCs via increased mitochondrial ROS.[303] Overall, while SIRT1, SIRT5, and SIRT6 seem to negatively affect senescence, there is contradicting literature on the effects of the other sirtuins on senescence.

Poly (ADP-ribose) polymerase 1 (PARP1) is another major NAD^+ consumer involved in the regulation DNA damage repair.[304] While not directly activated by dietary macronutrients, PARP1 can be affected by diet; high-fat diets induce the expression of PARP1, likely as a consequence of ROS generation and DNA damage,[305,306] and PARP1 deficiency exacerbates obesity.[307] SnCs develop a PARP1/NF-κB-mediated protumorigenic SASP.[308] The genetic depletion of a PARP1 activator, SREBP1c, accelerated adipocyte senescence.[309] PARP1 inhibition maintains NAD^+ levels and allows for normal SIRT1 function to protect against senescence,[310] potentially in the regulation of the DNA damage response.[311] Although PARP1 promotes senescence through depletion of NAD^+, the DNA repair activity of PARP1 likely plays a role in preventing DNA damage-induced senescence.

AMPK

AMPK is the primary regulator of ATP levels and is a AMP/ATP sensor that acts to maintain the energy balance within a cell.[312] CR increases the AMP:ATP ratio, leading the activation of AMPK.[257] Protein and glucose restrictions have also been shown to activate AMPK.[54,313] By contrast, high-fat diets inhibit AMPK.[220,314] Downregulation of AMPK activity induces premature senescence, while AMPK activation prevents premature senescence in MEFs, NIH3T3 cells, dental follicle cells, tendon stem/progenitor cell, human keratinocytes via maintenance of metabolic homeostasis, and murine skin.[315–320] Conversely, AMPK induces senescence in endothelial cells, colorectal carcinoma cells, and fibroblasts.[268,321,322] Persistent activation of AMPK accelerates senescence in a p53-dependent manner.[323] Additionally, SIRT1 protects cells from AMPK-induced senescence.[268] Therefore, AMPK has both pro-senescence and SASP-suppressive abilities. While NAD^+ may antagonize senescence, it may also promote SASP and senescence by activating p53 and NF-κB activity.[96,176] Interestingly, MR also upregulates AMPK to extend lifespan and reduce senescence in mouse kidneys.[156]

GH and insulin/IGF-1

Insulin/IGF-1 signaling axis is an evolutionarily conserved pathway that plays an important role in the regulation of metabolism, nutrition, and aging. In *C. elegans*, a mutation in *daf-2*, whose mammalian orthologue is the IGF1 receptor, was found to extend lifespan, which requires FOXO transcription factor *daf-16*.[54] Mice with reduced growth hormone (GH) have extended lifespan and also have decreased IGF-1, seemingly increasing insulin sensitivity and protecting from cancer and age-related diseases, suggesting that reduced insulin/IGF-1 signaling is crucial for healthspan and lifespan extension.[54] CR and carbohydrate restriction lead to decreased insulin/IGF-1 signaling, while fats are positively correlated with insulin/IGF-1 signaling.[324,325]

Insulin/IGF-1 signaling is implicated in senescence. Ames dwarf mice, which lack GH, have lower circulating IGF1 and insulin levels, leading to lower p21 protein expression in their pancreatic β-cells, consistent with the suppression of senescence.[326] IGF-1 itself also induces senescence in human fibroblasts, MEFs, 2BS cells, and mouse hepatic stellate cells in a p53-dependent manner[327–331] but may decrease senescence in endothelial progenitor cells from older humans.[332]

mTORC1

mTORC1 is highly conserved a central regulator of metabolism and aging, and genetic or pharmacological inhibition of mTORC1 signaling extends lifespan in organisms including mice (reviewed in Mannick and Lamming[333]). mTORC1 is highly responsive to environmental stimuli, such as amino acids, oxygen, and energy levels, as well as hormonal cues.[334]

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Pharmacological inhibition of mTORC1 by rapamycin extends lifespan in diverse species and has been shown to reduce the SnC burden and SASP expression in multiple mouse and human cells lines and in human skin.[66,169,333,335–339] mTORC1 promotes translation of IL1α to activate NF-κB, leading more SASP production.[66] mTOR also has been implicated in the cGAS-STING-mediated inflammatory response.[340] A mild increase in mTORC1 activity via a mutation in its complex also leads to increased senescence and SASP in multiple organs as well as shortens lifespan.[341] Steatotic hepatocyte-like extracellular vesicles can also induce hepatic stellate cell senescence *in vitro* via mTOR signaling.[342]

The dietary level of specific macronutrients regulates mTORC1 activity, with restriction of protein or BCAAs leading to lower mTORC1 activity.[148,152,343,344] Thus, nutrients can impact mTORC1-mediated senescence. Acquisition of senescence leads to constitutive upregulation of mTORC1 in human fibroblasts, making it resistant to both serum and amino acid starvation.[345] High-protein diets, which promote mTORC1 activity *in vivo* in mice, increase levels of senescence in the liver of C57BL/6 male mice.[153] In human HepG2 cells, BCAA supplementation enhances premature senescence via mTORC1.[174] In addition, 16-month-old male C57BL/6J mice given dietary BCAA supplementation for 12 months had increased pro-inflammatory gene expression in visceral WAT,[158] some of which overlap with common SASP markers. Consistent with this, BCAA accumulation within the cell promotes mTORC1-mediated SASP production in HEK293T cells.[172]

Other dietary macronutrients have been shown to activate mTORC1 activity, including carbohydrates. For example, in the context of pancreatic ductal adenocarcinoma, fructose induces mTORC1 activity.[346] Galactose also induces mTORC1 activity in MSCs and rodent skin.[196–198] Similarly, fats activate mTORC1. High-fat diets reduce AMPK phosphorylation, leading to increased mTOR activity, and are correlated with reduced SA-β-Gal staining in the hippocampus of mice.[220] Palmitate, saturated free fatty acid, activated mTORC1 in podocytes and hepatocytes.[347,348] This suggests that alterations of all types of dietary macronutrients may impact senescence via mTORC1 activity.

FOXO

The FOXO transcription factors are regulators of lifespan and tumor suppression, consisting of DAF-16 in *C. elegans*, dFOXO in *Drosophila Melanogaster*, and FoxO1, FoxO3, FoxO4, and FoxO6 in mammals.[349] FOXOs can be activated by CR and inhibited by consumption of excess sugars[350,351] and protect against HFD-induced fatty liver in mice.[352]

Different members of mammalian FOXO appear to have opposing roles on senescence. FOXO1 has promoting or inhibiting roles on senescence depending on the cell type. For example, inhibition of FOXO1 inhibited *p21* expression and senescence in an ovarian cancer cell line.[353] Knockdown of FOXO1 represses senescence in endometrial stromal cells[354] and normal human dermal fibroblasts.[355] In immune cells, FOXO1 opposes senescence to maintain stem-like properties in T cells.[356] Consistently, decreased FOXO1 expression in activated CD4+ T cells causes the development of senescent phenotypes, such as increased cell mass, preferential differentiation into effector T cells, and secretion of harmful exosomes.[357] FOXO3 is required for the lifespan extending effects of CR.[358] FOXO3a downregulation results in an increase in senescence in human dermal fibroblasts.[359] Consistently, deletion of FOXO3a accelerates the accumulation of senescence in response to cigarette smoke in mouse lung tissue,[360] while silencing of FOXO3 accelerates senescence in a human pluripotent stem cell-derived myotube model.[361] FoxO3 protects against senescence in H9c2 cells, a rat cardiomyocyte cell line, through the suppression of oxidative stress.[362] Consistently, FoxO3 deficiency increases senescence in cardiac microvascular endothelial cells, which is mediated by increased ROS generation.[363] FOXO3a also suppresses DNA double-strand break repair-induced mutations.[364] Taken together, these results suggest that FOXO3 mediates health and lifespan through the reduction of senescence.

FoxO4 is increased during senescence and plays a role in maintenance of the senescence phenotype and its viability.[365] In IMR-90 fibroblasts, a D-retro inverse isoform of FoxO4 (FoxO4-DRI) prevents the interaction of FoxO4 with p53 and promotes p53-mediated apoptosis, leading to improved organismal health.[365] In a human melanoma-derived cell line (Colo829), overexpression of oncogenic BRAF promotes ROS generation and activation of FOXO4, leading to increased p21-mediated senescence.[366] Additionally, stimulation of the JNK/FOXO4/MnSOD pathway accelerates senescence in human endothelial progenitor cells.[367]

While FOXO-mediated changes in senescence have not been shown in other model organisms, its homolog expression suggests it could have a potential role. For example, in *C. elegans*, high *daf-16* expression is correlated with an upregulation of genes involved in protection from oxidative stress, suggesting that *daf-16* may be protect against oxidative stress-induced senescence.[368] Though dFOXO has not been shown to directly impact senescence, overexpression of dFOXO in the fat body of the fruit fly *D. melanogaster* has been shown to extend lifespan.[369] All in all, this suggests that FOXOs, particularly mammalian FOXO1 and FOXO3a, oppose senescence to contribute to health and lifespan.

GCN2

General control nonderepressible 2 (GCN2) signaling is an ancient pathway that contributes to food preference and is part of the integrated stress response.[370,371] GCN2 is a kinase that binds to the ribosomal P-stalk to initiate translation when translation is slow, such as when there is a shortage of amino acids (i.e., PR and single amino acid restriction).[372,373] Recently, it was shown that the GCN2-FBXO22-mTOR pathway regulates amino acid sensing *in vitro* and *in vivo*.[374] The longevity extension in yeast due to amino acid starvation is reliant on GCN2.[375–377] GCN2 deletion in KURAMOCHI cells activates p53 and induces transcriptional targets such as *p21*,[378] which suggests that GCN2 may protect against senescence. Indeed, inhibition of GCN2 can lead to senescence in hepatocellular carcinoma cells under arginine deprivation.[379] While yeast require GCN2 in response to amino acid starvation and may protect against senescence, GNC2 is not absolutely required for the murine metabolic response to PR,[376] and the metabolic benefits of MR are mediated by a GCN2-independent noncanonical PERK (protein kinase R-like endoplasmic reticulum kinase)/NRF2 (NF-E2-related factor-2) pathway.[377] This suggests that

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while GNC2 signaling affects senescence, there are other pathways that likely mediate the effect of PR on senescence.

FGF21

Fibroblast growth factor 21 (FGF21) is a hormone that has important roles in regulating energy balance and glucose and lipid homeostasis.[380] It is induced in response to starvation or fasting and reduced protein intake.[149,381,382] FGF21 has been shown to extend lifespan when overexpressed and regulates mTORC1 in multiple tissues.[383,384] GCN2 is also required for FGF21 induction in response to PR.[54] FGF21 is required for the metabolic health and lifespan benefits of PR,[151] but is not required for the metabolic benefits of CR.[385] PR requires FGF21 to reduce renal inflammation,[386] suggesting that FGF21 may regulate senescence and its SASP. Consistently, *in vitro*, knockdown of FGF21 promotes accumulation of senescence, whereas FGF21 overexpression and/or administration have been shown to protect against senescence in bone marrow MSCs, endothelial cells, and mouse chondrocytes by promoting SIRT1 and inhibiting mTORC1 signaling.[387–390] A BACH1-dependent secretion of FGF21 reduces senescence in ferroptotic MEFs and extend lifespan in mice.[391] *In vivo*, FGF21 protects against adipose stem cell and hepatic senescence.[392,393] In the liver, this is mediated by the phosphorylation of AMPK and reduction of NF-κB expression produced from macrophages within the tissue.[393] However, the role of FGF21 on senescence in whole-body senescence has yet to be assessed.

Gaps in current knowledge

It is important to note that there is still limited evidence for dietary interventions affecting senescence in humans. Many of the papers cited in this review use cell culture systems or are conducted using model organisms, with very few performing whole organism studies or clinical studies. As senescence is heterogeneous, the effects of diet and nutrient-signaling pathways on senescence vary from tissue and cell type, making it difficult to draw definitive conclusions. In fact, interventions that delay or reduce senescence in one tissue could actually stimulate senescence in another. Also, there are very few studies that utilize heterogeneous mouse strains or genetically diverse mouse strains, such as the UM-HET3 and DBA mouse lines, respectively, to examine senescence. We emphasize the importance of such studies in the future of not only senescence research but all research aiming to impact human health. We recognize that translating these findings into effective dietary interventions for modulating cellular senescence in humans remains a challenge.

DISCUSSION

It is clear that senescence plays an important role in age-related diseases and that geroprotective dietary interventions may act in part by protecting against the accumulation of SnCs. SnC clearance can delay the onset of several age-related diseases and extend the lifespan of mice,[43,44] demonstrating the causal effects of senescence on aging. Here, we discussed how dietary interventions—in particular, the emerging class of dietary interventions that extend lifespan via regulation of specific dietary macronutrients—can regulate senescence through multiple nutrient-responsive mechanisms. Altering dietary macronutrients and/or nutrient-signaling pathways may provide new insights into the development or use of therapeutics that target senescence.

While abstemious regimens like CR, which require fasting and a reduced calorie intake, regulate SnCs, so do diets with reduced levels of macronutrients and their components. As we discuss here, dietary protein, carbohydrates, and fats all play a role in regulating SnCs in various tissues and cell types. These alterations in dietary macronutrients also engage different nutrient-responsive pathways that promote or protect against SnC burden.

While we know that many of the dietary macronutrient components can lead to senescence, there is still much left unknown, particularly when it comes to the physiological and molecular mechanisms by which these diets affect senescence. For example, while diets containing increased protein, glucose, or fats lead to increased senescence, it is unknown if these dietary components affect the rate at which cells become senescent or, alternatively, affect the rate at which SnCs are cleared. For example, altered levels of protein or specific AAs might impact DNA damage via increased genotoxic or oxidative stress or suppression of DNA repair mechanisms. Dietary fats, on the other hand, have been linked to exacerbating the SASP rather than directly to promoting senescence in the liver.[153] Do dietary intervention that extend health and lifespan, such as CR and PR, do so by protecting from DNA damage and reduce oxidative stress? With age, immune response strength and/or immune cell populations decrease,[394,395] suggesting that the immune system's ability to clear SnCs decreases with age as well. Do dietary components that induce an aged phenotype and shorted lifespan, such as WD, affect SnC clearance by aging the immune system? Conversely, do CR and PR extend health and lifespan by maintaining or improving the function of immune cell clearance of senescence? It should be evident from this extensive list of questions that we are only beginning to understand how dietary components regulate senescence and the accumulation, function, and clearance of SnCs.

Dietary regimens do not seem to optimally target SnCs, especially considering the complexity of the human diet and the potential for nutrients to interact with each other as well as interact with other dietary components. In contrast to the lab, humans consume a large variety of foods from different sources, which can result in a large variability in response to different dietary regimens. Senotherapeutic methods have been shown to have robust effects in reducing senescence as well as have shown improvements in health and lifespan in pre-clinical models.[46–50,52] Therefore, to maximize the therapeutic benefits of current senotherapeutics, diets should be taken into consideration. For example, rapamycin, which inhibits mTORC1 and extends lifespan, has been shown to have greater molecular effects in the context of high-protein diets, while metformin has the greatest molecular impact in the context of low-protein diets.[344] This suggests that the drug efficiency may be altered by the diet consumed. While the efficacy of senolytics has been tested in high-fat diets, their interactions with dietary protein or carbohydrates have not been examined.[48,207,213,396] Additionally, micronutrients have also been shown to have drug interactions, suggesting that this is a factor that needs to be considered as well (for a full review, see Karadima et al.[397]). As senolytics are now in human clinical trials,[398–401] it is important to consider

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the diets in which these individuals are consuming to maximize the benefits. For example, rapamycin, which acts as a senomorphic,[402] might have the biggest benefits for those eating a high-protein diet, and negligible benefits for individuals eating a low-protein diet. In line with this, senolytic drug efficacy has the potential to be altered by nutrient-responsive pathways. As the diets we consume trigger changes in nutrient-responsive pathways, the benefits of these drugs also will be altered in response to these pathways. If we use SnC burden as a metric of health, we may be able to alter senolytic dosage or even alter the senotherapeutic drug chosen depending on the diet of each individual, promoting individualized medicine.

Alternatively, an exciting avenue to pursue is also to create new senolytic drugs based on pathways altered in longevity-extending and senescence-suppressing diets. For example, FOXOs can be induced by CR or low sugar diets.[350,351] While usually grouped together, FOXO4 seemingly has a different effect on senescence, which may allow it to be used as a target to mediate senolysis. For example, the FOXO4-p53 interfering peptide has the potential to be a powerful senolytic drug used in humans. As stated above, an altered isoform of FoxO4 (FoxO4-DRI) prevents the interaction of FoxO4 with p53 and to promote apoptosis.[365] This peptide has now been shown to selectively clear SnC from mouse tissue and human chondrocytes *in vitro*.[365,399] This suggests that the next wave of senolytics drugs may include those which target nutrient-responsive pathways that promote senescence clearance.

Precision nutrigeroscience is a concept based on the emerging principle that there is no ''one size fits all'' intervention when it comes to diet, with multiple individual factors (context) determining the optimal diet for healthy aging of each person.[403] The results here, as well as other studies demonstrating the molecular interaction between drugs and diet,[344] suggest that considering the interaction of drugs with dietary composition will allow clearance of SnCs or suppression of the SASP, as well as healthspan overall, to be maximized.

In conclusion, dietary macronutrients and nutrient-signaling pathways clearly regulate senescence. However, further research into how these dietary components and their related nutrient-signaling pathways can impact senescence as well as further testing into whole organism senescence and genetically diverse strains are still required to gain new insights in understanding human aging. By better understanding senescence, whether through gaining insight into the attenuation of their induction or accumulation or by promoting their clearance, allows for their development for targeting SnCs either alone or in conjunction with senolytic drugs. Additionally, by taking a nutrigeroscience approach to reduce SnC burden, we can potentially maximize the therapeutic benefits of targeting SnCs. All in all, we still have a lot to learn when it comes to how diet, senescence, and aging intersect to impact healthspan.

ACKNOWLEDGMENTS

We thank Dr. Matthew Yousefzadeh for critical reading of the manuscript. The Lamming lab is supported in part by the NIA (AG056771, AG081482, and AG081482), the NIDDK (DK125859), and startup funds from UW-Madison. This work was supported using facilities and resources from the William S. Middleton Memorial Veterans Hospital. M.F.C. is supported by F31AG082504. The Robbins lab is supported in part by the NIH (AG056278, AG063543, AG062413, AG069819, AG076041, AG079754, AG076515, and AG081293) and grant ASAP-000592 from the ASAP Collaborative Research Network. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This work does not represent the views of the Department of Veterans Affairs or the United States Government.

DECLARATION OF INTERESTS

D.W.L. has received funding from and is a scientific advisory board member of Aeovian Pharmaceuticals, which seeks to develop novel, selective mTOR inhibitors for the treatment of various diseases. P.D.R. is a co-founder of Itasca Therapeutics, a new start-up developing novel senotherapeutics to extend human healthspan.

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Please cite this article in press as: Calubag et al., A nutrigeroscience approach: Dietary macronutrients and cellular senescence, Cell Metabolism (2024), https://doi.org/10.1016/j.cmet.2024.07.025

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Please cite this article in press as: Calubag et al., A nutrigeroscience approach: Dietary macronutrients and cellular senescence, Cell Metabolism (2024), https://doi.org/10.1016/j.cmet.2024.07.025

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