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Review Article

The effects of macronutrients metabolism on cellular and organismal aging

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ABSTRACT

Evidence supports the notion that metabolic pathways are major regulators of organismal aging, and that metabolic perturbations can extend health- and lifespan. For this reason, dietary interventions and compounds perturbing metabolism are currently explored as anti-aging strategies. A common target for metabolic interventions delaying aging is cellular senescence, a state of stable growth arrest that is accompanied by various structural and functional changes including the activation of a pro-inflammatory secretome. Here, we summarize the current knowledge on the molecular and cellular events associated with carbohydrate, lipid and protein metabolism, and define how macronutrients can regulate induction or prevention of cellular senescence. We discuss how various dietary interventions can achieve prevention of disease and extension of healthy longevity by partially modulating senescence-associated phenotypes. We also emphasize the importance of developing personalized nutritional interventions that take into account the current health and age status of the individual.

Introduction

Dietary interventions and aging

Aging is a major risk factor for non-communicable pathologies such as cancer, cardiovascular diseases, musculoskeletal dysfunctions and neurodegeneration. The aging process is characterized by complex molecular, cellular and tissue-level changes which lead to a gradual decline in functional capacity [1]. Studies in model organisms have demonstrated that diet has profound influence on aging rates, and that the nutritional status is directly correlated with the risk of age-associated morbidities [2]. Macronutrients are the primary constituents of foods and the source of calories which organisms consume in large amounts to meet energy demands and to promote growth. Macronutrients comprise three elements: carbohydrates, proteins, and fats. Through various metabolic pathways, macronutrients are digested into their basic building blocks: amino acids from protein, saccharides from carbohydrates, and fatty acids from fats [3]. Limiting general caloric intake without malnutrition by reduction of macronutrients intake, also known as calorie restriction, is a robust intervention shown to extend the health- and lifespan

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of several experimental animals, including rodents and non-human primates [4]. However, it is becoming more evident that not only the total amount, but also quality and relative proportions, of macronutrients play an important role in long-term metabolic health.

Aging and cellular senescence

Cellular senescence is a state of stable cell cycle arrest activated in response to stressors or developmental signals [5]. Although senescent cells do not divide, they remain metabolically active, continue to grow in size and develop a secretory phenotype termed senescence-associated secretory phenotype (SASP) [6]. Cellular senescence functions as a potent mechanism against tumorigenesis in a cell-autonomous manner [7]. In addition, senescent cells can play a pivotal role in optimal tissue regeneration, repair and embryonic development [8–10].

In contrast to these beneficial functions, chronic presence of senescent cells with a SASP can cause low grade sterile inflammation, leading to tissue dysfunction and degeneration [11]. In accordance with the contribution to the loss of tissue homeostasis by altering the function of neighboring cells, the clearance of senescent cells delays aging and increases lifespan in mice [12]. Cellular senescence may therefore be viewed as an elegant mechanism that preserves tissue function early in life but that becomes detrimental in older organisms [13]. Despite the considerable increase in studies that focus on cellular senescence in the last decade, there is no single marker that can be used for all types of senescent cells [14]. Multiple markers and molecular tools are available, and a combination of these markers is a preferred method for the identification of senescent cells [5,15]. The most commonly used markers are: high activity of the lysosomal senescence-associated beta-galactosidase (SA-β-gal) [16]; enhanced expression of cyclin-dependent kinase (CDK) inhibitors CDKN1A (p21) and CDKN2A (p16) [17], loss of the nuclear lamina protein lamin B1 [18]; secretion of biomolecules included in the SASP [6], and persistent DNA damage response which is preferentially located at telomeres [19].

Dietary macronutrients in longevity and cellular senescence

There is substantial evidence supporting the concept that metabolic pathways are major regulators of tissue and organismal aging, and that certain metabolic perturbations can lead to prolonged health and longevity. Interestingly, various dietary regimens and metabolic perturbations influence the accumulation of senescent cells and the development of the SASP. In the next sections, we provide an overview of the molecular and cellular events by which macronutrients modulate the induction of senescence-associated phenotypes, and outline the relevance of balancing macronutrient intake to reduce detrimental senescence-mediated effects on disease and aging.

Carbohydrates

Carbohydrates are used in different cellular processes, including cellular signaling and energy production. Glucose, which is the end product of many types of carbohydrates, has been extensively studied in terms of metabolism and influence on the aging process. In yeasts and nematodes glucose-enriched diets shorten lifespan [20]. In humans, the consumption of high glycemic index foods is correlated to the increased risk of different age-related diseases like type 2 diabetes (T2D) and cardiovascular diseases. For instance, a meta-analysis study concluded that diets with higher glycemic index (GI) and load are associated with a higher risk for developing T2D [21]. Mortality risk increases with high sugar intake [22], and glucose dysregulation is a major risk factor for many diseases associated with aging [23]. T2D is a significant risk factor for many age-related diseases (e.g., kidney, cardiovascular and neurodegenerative diseases) [24–26], suggesting that glucose dysregulation might accelerate biological aging. Notably consumption of a diet with low GI late in life extends the lifespan of mice [27]. Therefore, consumption of low GI food might be even more important at later stages in life as the body capacity to regulate glucose levels progressively declines with age [28].

One common hallmark of senescent cells is dysfunctional mitochondria, a state which leads to increased glycolysis as an adaptive process [29]. Many studies have shown that glucose consumption, glycolysis and lactate production are increased in senescent cells [30–32]. Because a major energy-consuming process of senescent cells is the SASP, it is likely that SASP levels are proportional to glucose availability. In agreement with this concept, circulating cytokines are acutely induced by hyperglycemia through oxidative stress mechanisms [33], and high GI carbohydrates increase the activation of NF-κB, a major inducer of the pro-inflammatory arm of the SASP [34]. p53 represses both glucose transport, by inhibiting a subset of glucose transporters, and lactate transport, by suppressing MCT1, and glycolysis through the induction of TIGAR or the inhibition of PGM [35]. Additionally, p53 suppresses several components of the SASP [6], suggesting that the SASP might be regulated, in part, by glycolysis.

Despite glycolysis being an important mechanism for glucose metabolism, it can potentially cause cellular injury due to increased production of toxic products, including methylglyoxal. Methylglyoxal is a dicarbonyls, and a potent glycating agent that can react with proteins, lipids and nucleic acids to form advanced glycation-end products (AGEs) [36]. Production of AGEs aberrantly increases during hyperglycemia [36] (Fig. 1). Since the senescence phenotype is accompanied by increased glycolysis, the aberrant accumulation of senescent cells might lead to the accumulation of methylglyoxal, and subsequent increased production of AGEs – a mechanism by which senescent cells could promote systemic dysfunctions and multimorbidity.

Glucose levels might not only modulate senescence-associated phenotypes, but also promote entry into a senescence state, as multiple pathways are implicated in

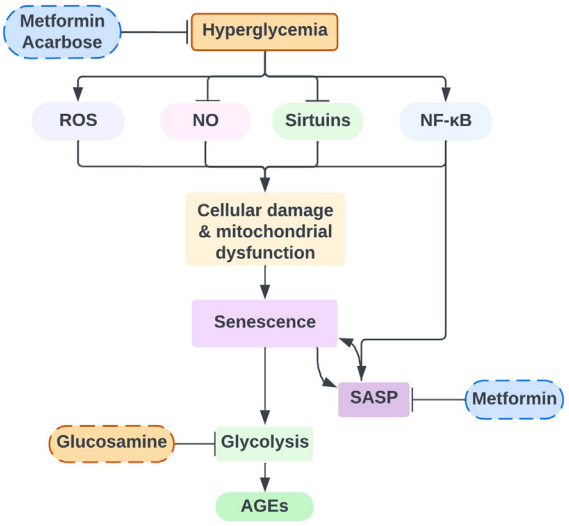

Fig. 1 Potential mechanisms through which hyperglycemia, as well as certain compounds (dashed border), may modulate the induction of cellular senescence. Abbreviations: ROS: reactive oxygen species; NO: nitric oxide; SASP: senescence-associated secretory phenotype; AGEs: advanced glycation end products.

hyperglycemia induced-senescence [37]. Direct induction of cellular senescence by hyperglycemia might be particularly relevant for cells able to uptake glucose without the action of insulin. For example, in endothelial cells glucose uptake mainly occurs via glucose transporter 1 (GLUT-1) in an insulin-independent manner [38]. High intracellular glucose concentration can stimulate the production of mitochondrial superoxide and ROS via glucose autoxidation, leading to cellular damage and damage-induced senescence [39]. Moreover, some studies have shown that hyperglycemia reduces nitric oxide (NO) production, which is known to interfere with the induction of cellular senescence [40,41]. Numerous experiments have also shown that downregulation of sirtuins (SIRTs) could be implicated in hyperglycemia-induced cellular damage. In accordance, hyperglycemia has been shown to downregulate the expression of SIRT3 and, consequently, promotes the induction of senescence [42] (Fig. 1). Interestingly, downregulation of SIRT3 leads to a type of senescence mediated by mitochondrial dysfunction termed "MiDAS" (Mitochondrial Dysfunction-Associated Senescence) which has a less pro-inflammatory signature [43]. Another sirtuin, SIRT1, was reported to protect endothelial cells from hyperglycemia-induced senescence, partially through the reduction of oxidative stress [44].

Glucose fluctuations with intermittent high glucose (IHG), which can occur after the consumption of high GI foods (i.e., postprandial spikes in blood glucose) and/or in diabetes, is detrimental for the integrity of endothelial tissue, and has been shown to induce senescence more robustly compared to constant hyperglycemia [45,46]. Hyperglycemia is associated with high AGEs production, and AGEs (e.g. glycated collagen) and dicarbonyls (e.g. Glyoxal and Methylglyoxal) induce senescence in endothelial cells [47,48] and kidney epithelial cells [49]. As a result, hyperglycemia can increase the number of senescent cells which can favor insulin resistance and type 2 diabetes further increasing a hyperglycemic state. This might create a vicious cycle where hyperglycemia and diabetes cause premature accumulation of senescent cells, and aberrant cellular senescence sustains pathology and accelerates tissue degeneration [50–53].

Some dietary carbohydrates are known to be indigestible but can be processed by the gut microbiome to produce different bioactive molecules with health-promoting effects [54]. Butyrate, a short chain fatty acid (SCFA) by-product of dietary fiber fermentation, was shown to downregulate inflammatory pathways in different conditions, including aging [55,56]. The potential effect of SCFA on senescence is described in the lipids section.

As glucose metabolism is a key player in the aging process, modulation of glucose consumption and metabolism has the potential to prevent tissue dysfunction and delay age-related decline. Based on human observational studies, the first-line drug for T2D, metformin, has gained interest as pharmacological intervention to extend human health and longevity [57], and it is currently under preparation for the first clinical trial on aging called TAME [58]. Interestingly, Metformin was shown to inhibit the SASP through interfering with NF-κB signaling [59]. However, many questions need to be answered concerning potential adverse effects, non-responders, and whether metformin has any positive effect on healthy individuals, including reducing the SASP [58]. Another diabetic control drug with an anti-aging potential is the α-glucosidase inhibitor acarbose. Acarbose and other α-glucosidase inhibitors alter the absorption of carbohydrates through the inhibition of their conversion into simple sugars in the intestine, leading to a reduction in postprandial glucose blood level [60]. Acarbose increases the levels of butyrate in both the colon and in serum [61,62], and its concentrations are associated with increased survival [63]. Additionally, acarbose was shown to reduce mTOR activity in different tissues [64,65]. In a recent study, acarbose was able to extend median and maximal lifespan and to improve various health parameters in genetically heterogeneous male and female mice [66]. As mentioned previously, glycolysis might promote tissue aging via promoting the formation of AGEs. Remarkably, D-glucosamine, which can act as a glycolysis inhibitor, was shown to possess longevity effects in aging mice [67]. Furthermore, it will also be interesting to assess whether the removal of senescent cells from aging organisms achieves health benefits due to the restoration of glucose homeostasis. Importantly, genetic and pharmacological removal of senescent cells was shown to alleviate the progression of both type 1 and type 2 diabetes [51,52,68].

Proteins

Proteins are complex molecules that assume a plethora of structural, metabolic, and signaling functions that are essential for cellular viability. Protein intake is emerging as a critical player in longevity. Moderate reduction of protein intake can extend healthspan and lifespan in different species [69]. The importance of dietary protein intake for longevity has been evaluated by the Geometric Framework for Nutrition [70]. Mice fed with a diet that is low in protein-to-carbohydrate (P:C)

ratio showed enhanced insulin sensitivity, improved metabolic health, slower aging, and extended lifespan, regardless of caloric intake. In contrast, diets with high P:C ratio worsen metabolic health, and negatively impact longevity [71,72]. In humans, a 6-week protein restriction (7–9% of energy intake) randomized controlled study in overweight adults resulted in improved metabolic parameters [73]. Additionally, in individuals aged between 50 and 65, low protein intake (less than 10% of calories from protein) has been linked to a significant decrease in the risk of all-cause and cancer-related mortality [74]. Okinawans, the longest living population in the world, are used to a dietary regimen with only 9% of calories derived from proteins, with a 9:85 ratio of protein-to-carbohydrate [75]. Although the restriction of proteins by a 1:10 ratio of protein-to-carbohydrate has been associated with extended longevity and prevention of various age-related diseases across many species [76], the type of dietary carbohydrate consumed can have an important impact on the metabolic health effects induced by a low protein diet [77]. In addition, individuals older than 65 consuming a low protein diet (<10%) exhibit increased mortality and old mice are not able to maintain their weight on a low protein diet, indicating that protein utilization is negatively affected by aging [74]. These results suggest that protein intake should be adjusted to life stage and balanced with the other macronutrients in order to achieve optimal health.

In addition to protein intake, protein source (i.e., animal or plant) might also have an impact on healthspan. Animal proteins are associated with a higher risk of mortality, especially from cardiovascular diseases, compared to plant proteins, which are associated with lower all-cause mortality [78]. In animal studies, casein was associated with a 5-fold increase in the risk of developing atherosclerosis compared to soy protein [79]. In a prospective study, postmenopausal women showed a 30% reduction in the risk for coronary artery disease mortality following an isocaloric replacement of animal with plant proteins [80]. The "Nurses' Health Study" and the "Health Professionals Follow-Up Study" showed that increased intake of animal proteins is linked to higher all-cause, cardiovascular, and cancer-related mortalities, whereas plant proteins were linked to lower all-cause and cardiovascular mortalities. These findings could be, at least in part, explained by the proportion of amino acids in animal versus plant proteins [78]. The restriction of certain amino acids, such as methionine and branched chain amino acids (BCAAs), can have a significant impact on health and lifespan in different experimental models. A randomized controlled study showed that a 6-week intervention of diets with a moderate protein restriction (7–9% of energy intake) was correlated with decreased BCAAs levels in plasma and improved metabolic parameters [73]. Mice fed a diet low in the BCAAs isoleucine and valine had an improvement in body composition and glucose tolerance [73,81]. Likewise, methionine restriction has been shown to extend lifespan in different model organisms from yeast to rodents [82]. With regard to protein composition, vegan and plant-based diets are naturally low in BCAAs and methionine, suggesting that such diets might extend healthy longevity [83].

The evolutionarily conserved insulin/IGF-1 signaling pathway plays an essential role in controlling lifespan [84]. Interestingly, low protein diets were associated with low

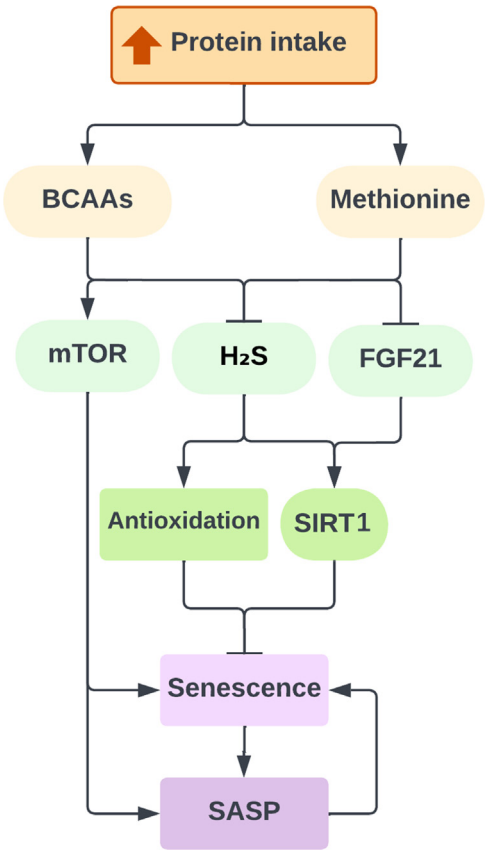

Fig. 2 An overview of how an increased intake of dietary proteins may induce cellular senescence, with particular focus on oxidation response and certain amino acids. Abbreviations: BCAAs: branched-chain amino acids; mTOR: mechanistic target of rapamycin; FGF21: fibroblast growth factor 21; SIRT1: sirtuin 1; SASP: senescence-associated secretory phenotype.

circulating levels of IGF-1, and decreased mortality and the incidence of cancer in subjects younger than 65 years [74]. The restriction of a single amino acid, such as methionine, was also shown to reduce plasma IGF-1 in mice [85]. Of note, prolonged exposure of cells to IGF-1 can regulate the SIRT1-p53 pathway and promote senescence [86], suggesting a potential delay in the accumulation of senescent cells in methionine-restricted dietary conditions (Fig. 2). Interestingly, we have recently shown that higher protein dietary content correlates with an increase in different senescence-associated markers in mouse liver [87].

mTOR signaling is known to have a major role in the aging process, and availability of branched-chain amino acids, in particular leucine and methionine, regulates mTORC1 activity [88] (Fig. 2). Interestingly, it has been suggested that mTOR signaling is a primary mediator of the conversion from a quiescent to a senescent state, a process that is defined as 'geroconversion' [89]. In addition, mTOR acts as a promoter of the secretory phenotype (SASP) in at least two ways. On one side, it increases the translation of IL-1α mRNA, which elevates inflammatory genes regulated by the transcription factor NF-κB [90]. On the other side, it interacts with MAPK

leading to an increase in the translation of the MK2 kinase, which consequently prevents the degradation of different SASP factor transcripts by ZFP36 ring finger protein-like 1 [91].

Rapamycin, an mTOR inhibitor, is able to significantly increase longevity in mice even when administered at a late-stage in life [92–94], in addition to reducing the SASP [90]. The Dog Aging Project, a longitudinal study of aging in companion dogs, has started a large-scale clinical trial involving the use of rapamycin in dogs for health and lifespan extension. The large-scale intervention study is based on the promising results of a short-term pilot study that showed an improved heart function in rapamycin-treated middle-aged dogs, compared to placebo [95]. Overall, these observations are encouraging the use of mTOR inhibitors to enhance human longevity. Conversely, prolonged rapamycin treatment may lead to potential adverse effects, such as glucose intolerance and immunosuppression. For this reason, intermittent dosing regimens have been proposed to reduce the adverse effects of rapamycin [96]. An alternative strategy can be the use of molecules that can specifically target mTORC1, given that many rapamycin-driven side effects are caused by its inhibition of mTORC2.

Another mechanism by which moderate protein restriction can enhance longevity is through the increase in the production of hydrogen sulfide (H_2S) [69]. Mammalian cells produce H_2S through the reverse trans-sulfuration pathway, where sulfur is transferred from homocysteine to cysteine, producing several sulfur metabolites in the process, including H_2S [97]. Homocysteine is produced from dietary methionine, and the former is used to generate cysteine through the action of the cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE, encoded by *CTH* gene) enzymes. Interestingly, CSE deficiency was shown to stimulate cellular senescence in mouse embryonic fibroblast (MEFs) [98]. MEFs isolated from CTH-KO mice showed elevated oxidative stress, reduced proliferative capacity, higher number SA-β-gal cells and increased levels of p53 and p21 compared to wild-type controls [98]. Sodium hydrosulfide (NaHS), a H_2S donor, reportedly reduced the protein levels of p53 and p21, levels of ROS, and the percentage of SA-β-gal-positive cells. These effects were attributed to the sulfhydration of Keap1 protein and the activation of Nrf2, which is a transcription factor that mediates the expression of antioxidant genes [98]. Another study showed that H_2S prevents H_2O_2-induced senescence in HUVECs by enhancing the activity, but not the levels, of SIRT1 [99] (Fig. 2). Similar findings were reported in the Hcy-induced neuronal senescence model using HT22 cells [100]. Interestingly, it was shown that the intracellular levels of H_2S are increased during cellular senescence due to an increased transcription of CTH [101]. Although H_2S could potentially suppress NF-κB by reducing the phosphorylation of IκBα and p65 subunit, it is yet to be determined whether the induction of H_2S in senescent cells can have a direct effect on senescence-associated phenotypes other than inflammation.

Fibroblast growth factor 21 (FGF21) is an insulin-sensitizing hormone associated with a better metabolic health and longevity [102]. Because FGF21 is induced by protein, BCAAs or methionine restriction, it has been suggested that the health-promoting effects of such interventions are in part due to the increase of circulating FGF21 [69]. It is interesting to note that vegan diets -which are intrinsically low in total proteins and in methionine and BCAAs- are associated with increased levels of FGF21 [83]. FGF21 can prevent or delay senescence induction in osteoarthritis via the increased expression of SIRT1 and subsequent inhibition of mTOR [103]. Additionally, it was shown that in endothelial cells, FGF21 is able to delay and prevent both replicative and premature senescence, respectively [104] (Fig. 2).

Lipids

Lipids constitute a broad category of essential water-insoluble biomolecules with crucial functions as energy sources, cellular membrane constituents and signaling molecules. Lipids are obtained primarily in the form of fatty acids, which normally occur in food sources in their esterified form (i.e., fats). After intake, fatty acids can either be used for energy production through mitochondrial β-oxidation or serve as building blocks for more complex lipid classes [105].

Excessive fat intake in humans is strongly associated with the increased prevalence of obesity and metabolic diseases. Studies on dietary fats have mainly focused on the total amount consumed or on the relative contribution to caloric intake. In animal models, high fat diets are frequently employed to study obesity, metabolic dysregulation and subsequent development of pathologies otherwise associated with aging such as diabetes, atherosclerosis or hepatic steatosis [106–109]. However, it is becoming increasingly clear that the quality of dietary fats and the balance between various macronutrients play a larger role in determining health outcomes than the absolute amount of fat consumed [110].

Reported negative health effects of high fat diets in humans broadly correspond to the issues generally associated with hypercaloric feeding and energy imbalance, with very little evidence that excess calories obtained from fat instead than from proteins or carbohydrates would have a more detrimental impact [110]. Foods with high fat content can be overconsumed due to high palatability and limited satiating capacity, and the high energy density of fats can lead to hypercaloric intake [111]. A comparative analysis of various experimental rodent diets indicated that the weight gain conventionally observed in mice maintained on a HF diet partly results from compensatory overfeeding elicited by limited intake of protein and carbohydrate [71]. However, medium chain triglycerides such as those found in coconut oil may be able to contribute to satiety and limit appetite [112].

Supporting the claim that HF diets are not detrimental *per se* is the positive health outcome of ketogenesis during aging. In conditions of limited carbohydrate availability, metabolism shifts towards increased beta oxidation with consequent production of beneficial ketone bodies such as beta-hydroxybutyrate [113]. Mice maintained on a ketogenic diet from middle age display an extended median lifespan [114], and male mice intermittently fed an isocaloric ketogenic diet exhibit improvements in longevity and limited cognitive and motor decline at old age [115,116]. Pilot studies have recently shown that ketogenesis is linked to improved cognition in aged patients suffering from HIV-associated neurocognitive impairment [117], and in individuals with mild cognitive impairment [118].

The qualitative composition of the lipid fraction of the diet is probably the most important factor pertaining to fat consumption, as different fatty acids have clearly distinct properties and physiological effects. The risk of habitual overfeeding and consequent weight gain is highest in the context of a diet rich in saturated fatty acids, which promote hypothalamic inflammation and dysregulation of feeding behavior [119]. Conversely, unsaturated fatty acids can reverse inflammatory processes in the hypothalamus and limit passive food intake [120]. Male Wistar rats fed diets with similar amounts of differently sourced fats exhibit profound differences in health and longevity. In this case, a sunflower-oil based diet resulted in a shorter medial lifespan and increased bone loss and liver fibrosis at old age compared to a virgin olive oil based (MUFA rich) or fish oil based (n-3 PUFA rich) diet [121]. Epidemiological studies indicate that a substitution of saturated fatty acid (SFA) with mono or polyunsaturated (MUFA or PUFA) without reduction of total fat intake, such as by adoption of a Mediterranean diet, is the best approach for addressing multiple cardiovascular risk factors (LDL-C, ApoB, ApoA-I and circulating triglyceride levels) [122]. Additionally, excess SFA can induce generalized inflammation via Tlr4-dependent macrophage polarization [123], while increasing MUFA levels may be able to counteract this phenomenon through PPARγ activation [124].

Different organismal lipid profiles are associated with age and health status, and their manipulation could alleviate age-related pathophysiological processes [125]. Nevertheless, it is difficult to estimate the extent to which dietary interventions are capable of such manipulation. Individual lipid profiles depend not only on nutritional fat input, but also on *de novo* lipogenesis and expression of enzymes acting on fatty acid chains in terms of saturation, elongation and incorporation into more complex lipid forms. PUFAs stand out in this regard, because their biosynthesis is impossible in mammalian cells and therefore must be obtained solely from the diet. Interconversion between different n-3 PUFA forms is possible but rate-limited, and ability to synthesize EPA from ALA declines with age [126]. It could therefore be argued that changes in the intake of PUFAs stand the highest chance of modulating lipid profiles through dietary means. Because *de novo* lipogenesis in mammals primarily results in the production of palmitic acid, it might be expected that excessive reliance on this process would shift the organismal lipid profile towards an unfavorable state. In line with this idea, a few studies indicate that diets with very low-fat composition lead to increased all-cause mortality [122].

During aging, the capacity of subcutaneous adipose tissue to store fat declines, and fat deposits migrate to ectopic locations with suboptimal abilities to control fatty acid release [127]. As a result, the levels of circulating free fatty acids increase with age and create a predisposition towards lipotoxicity. In this context, the aged organism could be particularly reliant on a good dietary balance between different fatty acids, since increased circulating levels, due to impaired storage in adipose tissue, can exacerbate both their beneficial and detrimental effects. High fat diet-induced obesity and dyslipidemia correlate with increased accumulation of multiple senescent cell types in various animal models [128,129], as well as in human patients [130]. It was shown that a high fat diet can induce senescence in mice, mainly in visceral adipose tissue, and that the elimination or prevention of senescent cells alleviates obesity-induced metabolic dysfunctions [51,131]. The need to store excess fat exerts mitotic stress on preadipocyte populations, ultimately leading to a massive increase in senescent cell burden in adipose tissue [127]. An upregulation of senescence markers was also shown in renal tubular cells of obese mice maintained on HF nutrition [132]. In the rodent brain, excessive exposure to dietary fat (and particularly palmitic acid) induces senescence and inflammation through an increase in oxidative stress paired with impairment of autophagy [133]. In a non-human primate model (baboons), a HF diet was able to induce premature endothelial cell senescence after only 7 weeks [134], indicating that development of obesity is not a prerequisite for the occurrence of detrimental health effects of high fat exposure. Excess palmitate exposure was also shown to induce senescence in endothelial cells in different studies [135,136]. Moreover, senescent adipocyte progenitor cells seem to impair adipogenesis via cell-autonomous mechanisms — by losing adipogenic capacity, triglyceride storage, and secretion of adipokines [137], and in a non-cell autonomous fashion through the secretion of activin A [138].

Due to the fact that lipid storage in adipocytes seems to be an important protective mechanism against lipotoxicity and metabolic disease [139], senescence-driven impairment of adipose tissue might play an important role in promoting metabolic dysregulations. Due to dysfunctional mitochondria, some types of senescent cells have also decreased capacity to efficiently catabolize fatty acids by β-oxidation. As a consequence, some senescent cells, such as hepatocytes and fibroblasts, accumulate excessive fat and become pathogenic [140] (Fig. 3).

The secretory output of senescent cells contributes significantly to the systemic pro-inflammatory milieu of the aged organism. The modulatory effects of individual fatty acids on inflammation have been studied primarily in terms of mechanisms involving immune cells. Nevertheless, it could be argued that in tissues and organisms with a high senescence burden, large shifts in inflammatory status would not be easily achievable without involvement of senescent cell responses. Detailed studies are still needed to explore the mechanistic influence of different fatty acids on SASP regulation, while some indicators are already arising from present research endeavors. As mentioned previously, senescence markers were increased in mice liver fed diets enriched in protein, but pro-inflammatory secretory markers were further enhanced in diets rich in fat content, suggesting the possible involvement of fatty acids in SASP regulation [87]. The intense secretory activity of some senescent cells is partly sustained through increased β-oxidation [141,142]. Based on transcriptional data indicating an upregulation of fatty acid synthase in senescent cells, concomitant with increased expression of enzymes participating in fatty acid oxidation and down-regulation of stearoyl-CoA desaturase, it has been suggested that saturated fatty acids represent the major energetic substrate in senescence [142]. It is possible that high availability of SFA could support an elevated production of SASP components, which would be compatible with the described pro-inflammatory effects of high SFA consumption.

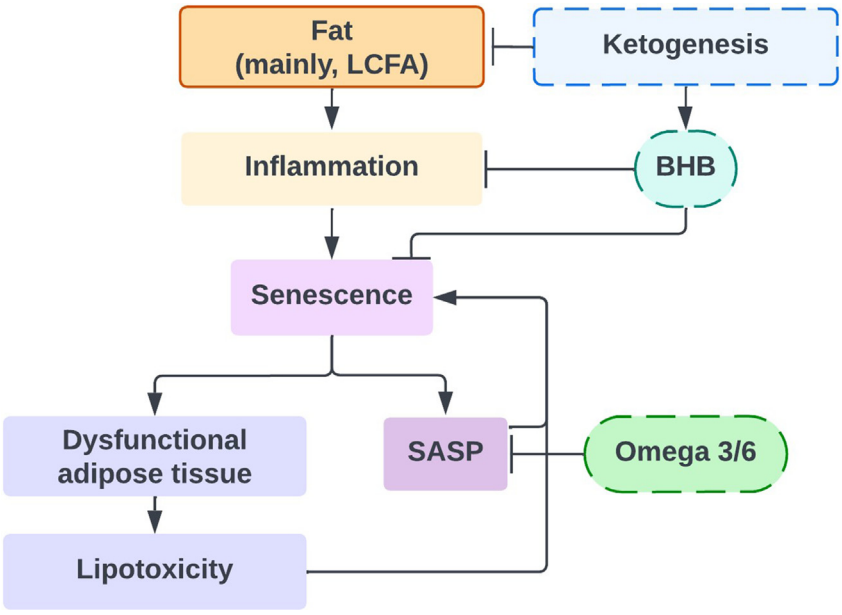

Fig. 3 A diagram showing how the intake of dietary fats, as well as certain interventions (dashed border), may induce inflammation and cellular senescence.
Abbreviations: LCFA: long-chain fatty acid; BHB: β-hydroxybutyrate; SASP: senescence-associated secretory phenotype.

Interestingly, PUFAs constitute the backbone for synthesis of oxylipins, representing the lipid fraction of the SASP [143]. It is unlikely that oxylipin production would be significantly responsive to overall nutritional availability of PUFAs, since senescent cells employ mechanisms to increase their efficiency of PUFA uptake (CD36 upregulation) [144] and PUFA release from cellular membranes (increased phospholipase A2 activity) [145]. In this context, a reduction of PUFA intake would be more likely to exert detrimental effects on neighboring healthy cells rather than limiting senescent cell activity. Nevertheless, the ratios between n-6/n-3 PUFAs might be able to modulate the composition of the senescent secretome in ways similar to those described for healthy cells, by entering different metabolic pathways. In recipients of kidney transplant, supplementation with marine n-3 PUFAs decreases plasma levels of multiple SASP factors including GCSF, IL1α, MMP-1 and MMP-13 [146]. n-3 PUFAS have been shown to limit the inflammatory responsiveness of macrophages by regulating the recruitment of Toll-like receptors to lipid rafts [147,148]. It is conceivable that similar mechanisms might operate in senescent cells, where Tlr2 participates in SASP regulation.

In contrast to saturated long-chain fatty acids, short-chain fatty acids (e.g., butyrate) were shown to have a plethora of beneficial effects, including anti-inflammatory properties [149]. Intriguingly, a related molecule with a strong chemical similarity, β-hydroxybutyrate (BHB), is the most abundant ketone body found in humans. BHB is mainly produced in the liver via fatty acid oxidation, and its production is enhanced in conditions where glucose is insufficient, such as fasting and exercise, in order to be used as an alternative energy source [150]. BHB is thought to have anti-aging properties [151]: on one side, it has a protective effect against the induction of senescence through upregulation of OCT4 and subsequent increase in Lamin B1 [152], which is an important protein that protects cells from damage by inducing a quiescent state [153]; on the other side, it is able to suppress oxidative stress [154] and attenuate inflammation [132,155], suggesting a potential role in modulating the pro-inflammatory arm of the SASP. Notably, some studies have demonstrated the beneficial properties of ketogenic diets on longevity [114,115] which might be, at least in part, driven by high BHB levels (Fig. 3).

Future directions

As discussed in this review, cellular senescence can be considered both a cause and a consequence of metabolic dysregulations, and perturbations affecting macronutrients metabolism can influence aging and longevity partly through modulating either the entry into a senescence state or different senescence-associated phenotypes, in particular the pro-inflammatory arm of the SASP. Dietary interventions represent a promising measure to prevent cellular and organismal aging, thereby preventing or delaying a plethora of age-related diseases. Nevertheless, the design of such interventions, and whether they can be combined with anti-senescence strategies, is a poorly understood area of research.

Based on the current literature, some links between certain dietary choices, age-associated mechanisms and the consequences for health and longevity are emerging. For example, high protein intake is linked to increased mortality possibly due to premature induction of pro-aging and pro-SASP mechanisms such as the IGF1 and the mTOR pathways [71]. Simultaneously, protein intake is crucial for the preservation of muscle mass and adequate intake is required to prevent age-associated muscle loss. The source of protein may also be

important in this context, as protein derived from plants contain a composition of amino acids that can promote longevity compared to protein derived from animal sources [83]. Foods with high GI can cause elevated levels of blood glucose and insulin, specifically postprandial [66], and high fat diets with abundant intake of carbohydrates can cause lipotoxicity, which can lead to various metabolic dysfunctions and the premature induction of senescence [51,131,156].

Interventions such as calorie restriction, ketogenic diet, and fasting might affect many of the aforementioned pathways and promote health [157]. Interestingly, calorie restriction can limit the accumulation of senescent cells in both mice and humans, suggesting that its pro-longevity properties might be, at least in part, due to reduced burden of senescence [158,159]. From a practical point of view, however, neither calorie restriction nor ketogenic diets are easy to follow. While fasting might represent a more feasible approach, the effects of specific fasting regimens on cellular and organismal senescence is still unknown in humans [160]. Studies in model organisms have suggested that treatment with certain regulators of metabolic pathways, such as metformin, acarbose, and rapamycin, represents a promising strategy to achieve pro-longevity effects, partially by modulating senescence-associated phenotypes, and could possibly be applied to humans [58,96]. Doubtlessly, the best results can be obtained by combining different interventions, whether targeting metabolism or senescence, in a personalized manner. Therefore, there is an urgent requirement in the field for developing strategies and biomarkers that can be used to measure biological age and to assess the efficacy of the applied interventions.

Conflict of interest

MD is the scientific co-founder of Cleara Biotech and is member of the scientific advisory board of Oisin Biotechnologies.

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