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**Title: The role of dietary strategies in the modulation of hallmarks of aging**

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## **Abstract**

The hallmarks of aging constitute an interconnected network of basic mechanisms that modulate aging and can be modulated by lifestyle factors, including dietary strategies. This narrative review aimed to summarize the evidence on promoting dietary restriction or adherence to specific dietary patterns on cellular hallmarks of aging. Studies with preclinical models or humans were considered. Dietary restriction (DR), usually operationalized as a reduction in caloric intake, is the main strategy applied to study the axis diet-hallmarks of aging. DR has been shown to modulate mainly genomic instability, loss of proteostasis, deregulating nutrient sensing, cellular senescence, and altered intercellular communication. Much less evidence exists on the role of dietary patterns, with most of the studies evaluating the Mediterranean Diet and other similar plant-based diets, and the ketogenic diet. Potential benefits are described in genomic instability, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, and altered intercellular communication. Given the predominant place of food in human life, it is imperative to determine the impact of nutritional strategies on the modulation of lifespan and health span, considering applicability, long-term adherence, and side effects.

**Keywords:** hallmarks of aging; food intake; fasting; dietary patterns; caloric restriction

## **Introduction**

Aging is a complex, biological malleable phenomenon and is considered the main risk factor for most chronic conditions and diseases (Sierra, 2016). This assumption constitutes the basis of geroscience, a research field born under the hypothesis that the basic mechanisms driving aging and age-related diseases overlap (López-Otín et al., 2013). In 2013, López-Otín et al. proposed nine molecular, cellular, and systemic hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín et al., 2013). An update was recently published by the author with the addition of three hallmarks. In fact, the new hallmarks were already included as a component of one of the nine initially proposed hallmarks of aging. “Disabled macroautophagy” was a specific case of loss of proteostasis, and “chronic inflammation” and “age-associated dysbiosis” were part of the “intercellular communication” (López-Otín et al., 2023). In common, all hallmarks are time-dependent on the aging process and can be manipulated by laboratory experiments to accelerate or by therapeutic interventions to slow down the aging process (López-Otín et al., 2023).

In the last decade since the first proposal, robust evidence has been published and extended to mammalian models and humans on the impact of a variety of compounds, drugs, and lifestyle factors, including diet strategies such as dietary restriction and dietary patterns (López-Otín et al., 2023; Malcomson and Mathers, 2018). Dietary restriction can be promoted by reducing total diet content, fasting, or restricting the intake of specific nutrients (Malcomson and Mathers, 2018), resulting in lifespan extension through evolutionary mechanisms and phenotypes that ensure survival under starvation periods (Franceschi et al., 2018). For another perspective, the assessment of dietary patterns allows assessing the role of the overall diet in preventing or ameliorating age-related diseases (Shannon et al., 2021). Dietary restriction and plant-based dietary patterns have been associated to improvements in common relevant clinical outcomes during aging, especially body composition changes (Forni et al., 2019; Ooi et al., 2020; Teng et al., 2013), glycemic control and insulin sensitivity (Forni et al., 2019; Heilbronn et al., 2006; Papamichou et al., 2019; Qian et al., 2019), lipid profile (Chiavaroli et al., 2018; Teng et al., 2013), blood pressure (Ndanuko et al., 2016; Ooi et al., 2020; Teng et al., 2013), lipid peroxidation (Ooi et al., 2020; Teng et al., 2013), inflammation (Barbaresko et al., 2013; Fontana et al., 2018b; Forni et al., 2019; Ooi et al., 2020), and cardiometabolic risk (Chiavaroli et al., 2018; Forni et al., 2019); although the mechanisms are not fully elucidated.

This narrative review focuses on the role of dietary restrictions and dietary patterns as potential nutritional strategies to modulate the nine hallmarks of aging proposed in the pioneering manuscript by López-Otín et al.

### **Research strategy**

Although this is a narrative review, a search was performed in the PubMed database between November 2021 and August 2022 to avoid missing important studies in this field. The keywords used to describe the dietary restriction included “low carbohydrate” OR “carbohydrate restriction” OR “low fat” OR “fat restriction” OR “low protein” OR “protein restriction” OR “fasting” OR “energy restriction” OR “caloric restriction” OR “dietary restriction”. For the search on the role of the dietary patterns the following keywords were used: “food groups” OR “dietary pattern” OR “ketogenic diet”. The search result for each dietary strategy was combined with keywords related to each of the nine hallmarks of aging using the Boolean operator “AND” and are presented below:

**Genomic Instability:** “genomic instability” OR “genetic instability” OR “genome instability” OR “DNA damage” OR “DNA lesions” OR “DNA instability” OR “DNA mutation” OR “mtDNA mutations” OR “mtDNA damage” OR “progeria”.

**Telomere attrition:** “telomere attrition” OR “telomere length” OR “telomere shortening”.

**Epigenetic alterations:** “epigenetic alterations” OR H4K16ac OR H4K20me3 OR H3K4me3 OR H3K9me OR H3K27me3 OR HP1 $\alpha$  OR NuRD.

**Loss of proteostasis:** chaperone OR HSF-1 OR Hsp70 OR Hsp72 OR “heat shock” OR “autophagy-lysosomal” OR “ubiquitin-proteasome” OR “loss of proteostasis”.

**Deregulated nutrient sensing:** “deregulated nutrient sensing” OR “insulin and IGF-1 signaling” OR IIS OR mTOR OR AMPK OR SIRT1.

**Mitochondrial dysfunction:** “mitochondrial dysfunction” OR “dysfunctional mitochondria” OR “mitochondrial decline” OR mitohormesis.

**Cellular senescence:** “cellular senescence” OR SABG OR “senescence associated secretory phenotype” OR P16INK4a OR P19ARF OR “INK4a/ARF” OR p53.

**Stem cell exhaustion:** “stem cell exhaustion” OR “stem cell decline”.

**Altered intercellular communication:** “altered intercellular communication” OR inflammaging OR “neuroendocrine dysfunction” OR immunosenescence OR “NLRP3 inflammasome” OR “NF- $\kappa$ B” OR “bystander effects”.

When the search resulted in a large number of studies (as the in case of genomic instability), the additional keyword “aging” was added to narrow the search. Additional studies were selected from the reference list of retrieved articles.

### **Selection criteria**

Only articles published in English and conducted with animal models or humans were considered. For the studies with animal models, the retrieved manuscripts used biomarkers of the hallmarks of aging as primary outcomes and clearly described the methods. For the studies with humans, only clinical trials and longitudinal studies were included. An exception was made for a cross-sectional study on the role of dietary restriction in cellular senescence. This is due to the lack of studies and considering that this work was conducted with participants from caloric restriction cohorts (supplementary table 7). In addition, only works with adults or older adults were included, without sex restriction. Both the search and selection of the manuscripts were conducted by N.A.G.F under the supervision of P.S.B.

### **Genomic instability**

Genomic instability “is the natural tendency of genomes to undergo alterations under physiological conditions” and is speculated to be central in the mechanism of aging (Vijg and Suh, 2013). Exogenous agents, but especially endogenous threats, as reactive oxygen species (ROS), can affect DNA integrity and stability (López-Otín et al., 2013; Vijg and Suh, 2013). The damage in both nuclear and mitochondrial DNA (mtDNA) can be reversible by DNA repair and maintenance systems; however, with aging these systems are overwhelmed and less efficient, resulting in the accumulation of genomic damage and ectopic DNA in the cytosol (López-Otín et al., 2023).

### **Genomic instability and dietary restrictions**

#### ***Preclinical models***

An attenuation of nuclear DNA damage and an increase in DNA repair is observed in rodents submitted to 30% to 55% CR (Drew et al., 2003; Kaneko et al., 1997; Kisby et al., 2010). CR could reduce the oxidative damage of DNA by decreasing mitochondrial H<sub>2</sub>O<sub>2</sub> production and free radical leak in complex I of mtDNA (Gredilla et al., 2001; López-Torres et al., 2002; Sanz et al., 2005). This amelioration of DNA oxidative damage seems to happen even when restriction begins late in life (Sanz et al., 2005). Furthermore, CR induces DNA

repair and maintains a functional genome by stimulating expression of DNA repair genes (e.g. Rad50, Rad21) (Lee et al., 2002), delaying age-dependent decline in apurinic/aprimidinic endonuclease (APE) (Kisby et al., 2010), and promoting autophagy (Hewitt et al., 2016). However, it is noteworthy that studies conducted with species other than rodents, such as fruit flies (*Drosophila*) (Edman et al., 2009), fish (ayu fish) (Nagasaka et al., 2005), and monkeys (Moore et al., 2007), did not find any impact of CR on DNA repair or DNA damage.

Another intervention includes restriction of 40% to 55% of total protein (Gedik et al., 2005; Sanz et al., 2004; Tanrikulu-Kucuk and Ademoglu, 2012) or 20% of methionine (Bárcena et al., 2018; Naudí et al., 2007; Tanrikulu-Kucuk and Ademoglu, 2012). In rats, restricting protein without changing caloric content resulted in decreased hepatic 8-Hydroxydeoxyguanosine (8-oxodG), a marker of oxidative DNA damage (Sanz et al., 2004; Tanrikulu-Kucuk and Ademoglu, 2012), and lower mitochondrial H<sub>2</sub>O<sub>2</sub> production (Sanz et al., 2004). Specifically, in methionine, its restriction could decrease oxidative damage to DNA (Naudí et al., 2007) by regulating groups of genes related to DNA repair, p53 pathways and inflammation (Bárcena et al., 2018).

### ***Human studies***

Different CR strategies resulted in reduced DNA damage in adults after 6 months of intervention demonstrated by shortest comet tail moment (indicator of DNA fragmentation). CR strategies included 25% CR, or 12.5% CR plus 12.5% increase in energy expenditure by promoting exercises or very low calorie diet (890 kcal/d) (Heilbronn et al., 2006).

Another strategy is the Muslim Sunnah fast, which consists of fasting between sunrise and sunset two days a week. This fasting strategy was associated with a reduction in DNA damage in adults and older adults (decrease % of DNA in the tail and tail moment) as early as 6 weeks (Teng et al., 2013). Sustained effects were observed even after 36 months of follow-up (Ooi et al., 2020) and most of the CR was mild (~18%) (Ooi et al., 2020; Teng et al., 2013).

## **Genomic instability and dietary patterns**

### ***Preclinical models***

The impact of a ketogenic diet (KD) has been tested in rodents, and the little evidence available supports this diet in reducing DNA oxidative damage. This was demonstrated by

lower levels of 8-oxodG and the enzyme PARP-1 (a DNA damage sensor) in rodents on a KD compared to a high carbohydrate diet (Elamin et al., 2018).

### ***Human studies***

Adherence to the Mediterranean diet (MedDiet) has been associated with lower concentrations of 8-oxodG in older adults (Gutierrez-Mariscal et al., 2012; Mitjavila et al., 2013). In a clinical trial of postmenopausal women with metabolic syndrome, one-year of MedDiet with additional olive oil (1L/week) or extra nuts (15, 7.5 and 7.5 g/d of walnuts, almonds and hazelnuts, respectively) resulted in a greater reduction in urinary 8-oxodG compared to controls (Mitjavila et al., 2013). Another clinical trial with older adults of both sexes showed that 4 weeks of MedDiet decreased plasma 8-oxodG when compared to a diet rich in saturated fatty acids (Gutierrez-Mariscal et al., 2012).

### **Summary on nutrition and genomic instability**

Cumulative evidence suggests that restricting energy intake or dietary protein/methionine may attenuate oxidative DNA damage. In humans, this benefit could be achieved by applying less or more restricted CR strategies, or by practicing intermittent fasting. With respect to the whole diet, an improvement in oxidative DNA damage was demonstrated when greater consumption of a MedDiet, which includes lower intake of red meat. In this sense, the impact of adherence to the ketogenic diet is still controversial.

### **Telomere attrition**

Hayflick limit telomeres are complexes of eukaryotic chromosomes that form a cap at the chromosome ends, protecting them from threats to DNA stability that can damage the informational genetic coding sequence (Blackburn et al., 2015; Turner et al., 2019). Throughout life, telomeres naturally shorten with each cell cycle (Blackburn et al., 2015; Turner et al., 2019); however, beyond the critical limit of the Hayflick threshold, telomere shortening induces DNA damage signaling that leads to cellular senescence and limits growth and repair capacity (Turner et al., 2019). Chronological age accounts for less than 10% of human telomere length variation, highlighting the influence of non-genetic factors (Blackburn et al., 2015). The assessment of telomere length is considered a biomarker for several age-related diseases and a target for clinical interventions (von Zglinicki and Martin-Ruiz, 2005).

### **Telomere attrition and dietary restrictions**

### ***Preclinical models***

In planarians (*S. mediterranea* asexual strain), it was observed longer telomeres after 20 days of starvation, depending on the *mammalian* target of rapamycin (mTOR) (Iglesias et al., 2019). In rodents, however, restricting the diet do not clearly prevent telomere shortening. Although 40% CR for 22 months resulted in reduced telomere shortening and telomere damage in young mice (Vera et al., 2013), a less evident impact occurred when CR was performed for a shorter period (8 to 16 months) (Al-Ajmi et al., 2014; Makino and Maeda, 2021). Furthermore, in rats with type 2 diabetes, CR did not preserve telomere length, although there was an increase in telomerase activity (Makino and Maeda, 2021). Regarding specific nutrients, while carbohydrates were found to be the main driver of telomere length (Gokarn et al., 2018), the protein was correlated with shorter telomere length in liver DNA (Gokarn et al., 2018; Tanrikulu-Kucuk and Ademoglu, 2012). The amino acids profile needs to be taken into account, however, as a positive correlation between non-essential amino acids (asparagine, glutamate, and taurine) and telomere length ratio has been reported (Gokarn et al., 2018).

Methods for assessing telomere length varied across studies (Supplemental table 2), some using the terminal restriction fragment (TRF) (Makino and Maeda, 2021; Tanrikulu-Kucuk and Ademoglu, 2012) and others fluorescence *in situ* hybridization (FISH) (Al-Ajmi et al., 2014, p.; Iglesias et al., 2019; Vera et al., 2013) or quantitative PCR (qPCR assay) (Gokarn et al., 2018; Iglesias et al., 2019). These methods differ in sensitivity, which may imply inter- and intra-individual heterogeneity (Baird, 2005).

### ***Human studies***

The impact of CR on telomere attrition in humans is unclear, with little evidence suggesting a potentially harmful effect. Adults and older adults ( $55 \pm 14.5$  years old) participants of the CR Society International, who had been on average 10 years on a CR regimen but without malnutrition, had shorter telomeres in peripheral blood mononuclear cells (PBMCs) than the control group (Tomiyama et al., 2012).

Among overweight and obese premenopausal women, although a first moment restrained eating was associated with greater telomerase activity (delay in telomere shortening), this relationship lost significance when % fat intake was included in the model (Daubenmier et al., 2012). In this sense, the hypothesis was raised that strategies that have a clear influence on the perception of deprivation may favor a change in diet content towards

higher consumption of fatty foods in substitution of carbohydrates sources. Such a change could imply accelerated telomere attrition through increased oxidative stress and inflammation (Daubenmier et al., 2012).

## **Telomere attrition and dietary patterns**

### ***Preclinical models***

Our literature search found no studies on the effect of dietary patterns on telomere attrition in preclinical models.

### ***Human studies***

Most of the evidence for dietary patterns in telomere attrition comes from observational studies. In a study with a cohort of Korean adults and older adults, a prudent dietary pattern was associated with longer telomere length in leukocytes (LTL) after 10 years of follow-up (Lee et al., 2015). Looking for the components of this diet, while the intake of legumes, nuts, seaweed, fruits, dairy, and coffee were positively associated with telomere length, the opposite was observed for the intake of red or processed meat, and sweetened carbonated beverages (Lee et al., 2015). Given these results, it seems plausible that the MedDiet could positively impact telomere attrition.

In fact, interventions based on MedDiet guidelines, lasting one (Fernández de la Puente et al., 2021; Gomez-Delgado et al., 2018) to five years (García-Calzón et al., 2015), have resulted in longer telomeres in adults over age 50. This effect seems to be independent of energy intake (Fernández de la Puente et al., 2021, p. 1), but influenced by genetic variations. After 5 years, the intake of MedDiet prevented telomere shortening and improved telomere length, but only among those carrying the Ala allele of the peroxisome proliferator-activated receptor  $\gamma 2$  gene (PPAR $\gamma 2$ ). Additionally, it was already observed an interaction between plasmatic monounsaturated fat acid (MUFA) and the single nucleotide polymorphisms (SNPs) near telomerase RNA component gene (TERC) during a MedDiet intervention, resulting in a greater LTL (Gomez-Delgado et al., 2018).

## **Summary on nutrition and telomere attrition**

Telomere length is usually measured in circulating leukocytes, and the effect of dietary interventions is far from clear. Preclinical models suggest a potential benefit of restricting 30% of energy intake on telomere length or telomerase activity, although there is a great variability in assessment techniques, making stronger conclusions difficult. On the other

hand, human studies indicate a greater potential for diet composition, with lower intake of fats, meats and sweets, and greater adherence to a MedDiet potentially contributing to the maintenance of telomere length.

### **Epigenetic alterations**

Epigenetics involve mechanisms that lead to heritable modifications to the genome without changing the DNA sequence itself (Waddington, 2012). Epigenetics mechanisms whose changes contribute to aging include DNA methylation, translational histone modifications, aberrant chromatin remodeling, and modifications via non-coding RNAs (López-Otín et al., 2023). Both global DNA hypomethylation and hypermethylation of some specific genes are associated with carcinogenesis and DNA instability (Rodríguez-Miguel et al., 2015), as well as with aging (Ashapkin et al., 2019). Epigenetic factors are reversible (Gong et al., 2015), and diet is suggested as a key determinant of lifespan in the context of this hallmark of aging (Malcomson and Mathers, 2018; Sen et al., 2016).

### **Epigenetic alterations and dietary restriction**

#### ***Preclinical models***

30% CR reversed age-related changes in methylation of some histones in mice brain (Gong et al., 2015). Under food deprivation (either CR or fasting), the histone demethylase domain-containing protein-3 (JMJD3) is activated and epigenetically upregulates genes involved in autophagy (Byun et al., 2020; Seok et al., 2018). Selective activation of genes by JMJD3 is mediated by the tri-methylation histone H3 at lysine 27 (H3K27me3) (Byun et al., 2020; Seok et al., 2018). In addition, there is a decrease in brain histone content with aging that can be counteracted by 30% CR (Gong et al., 2015).

Regarding protein, compared to a normal protein intake (21%), a diet with 7% protein (without CR) was able to reduce the expression of the methyltransferase EZH2 and the H3K27me3, resulting in tumor growth inhibition (Fontana et al., 2013). Most attention has been given to the restriction/repletion of one-carbon donors, especially the amino acid methionine (Malcomson and Mathers, 2018). Methionine deprivation is suggested to induce changes in histone methylation in mice (Mentch et al., 2015).

#### ***Human studies***

In a small sample of 12 adult Spanish women (20-40 years) with overweight/obesity,

30% CR for 8 weeks was able to induce changes in DNA methylation in 4 of the 5 genes assessed in PBMC cells. The most prominent results were observed in *CD36*, which encodes a membrane glycoprotein involved in lipid metabolism in humans (do Amaral et al., 2014). However, the authors ponder that the observed changes in DNA methylation may are not sufficient to influence the regulation of gene expression (do Amaral et al., 2014). A conclusion corroborated by the study of Mentch et al., in which although it was observed epigenetically changes induced by the restriction of methionine in mice, in humans, the achieved concentrations of serum methionine seems to be insufficient to induce changes in methylation (Mentch et al., 2015).

## **Epigenetic alterations and dietary patterns**

### ***Preclinical models***

The type of fat seems to exert some influence on epigenetic pathways, especially on DNA methylation and histone modifications. Young and adult mice fed a diet enriched with olive-oil showed greater overall DNA methylation in the mammary gland and tumor when compared to a group that received a low-fat diet. This global DNA hypermethylation has been associated with mechanisms that impede the progression of tumorigenesis, neoplastic transformation, and chromosomal instability (Rodríguez-Miguel et al., 2015).

On the contrary, hypermethylation in the promoter regions of tumor suppressor genes (*RASSF1A* and *TIMP3*) was observed with a corn oil-enriched diet. Hypermethylation of *RASSF1A* and *TIMP3* genes is probably due to increased DNA methyltransferase (DNMT) activity and is related to carcinogenesis (Rodríguez-Miguel et al., 2015). Since, compared to a low-fat diet, a higher intake of olive oil also increased DNMT activity, it is hypothesized that some components of olive oil, such as phenolic compounds, may counteract the harmful effect of a high-fat diet (Rodríguez-Miguel et al., 2015).

### ***Human trials***

To evaluate the effect of 18 months of MedDiet adherence and a low-fat diet, with or without physical activity, on DNA methylation, a series of studies was performed with a sample of 120 adults (92% men), with abdominal obesity or dyslipidemia (Keller et al., 2020; Yaskolka Meir et al., 2021a, 2021b). In general, there was a smaller impact of the diet and a greater difference in the pattern of DNA methylation according to the response to the

intervention in terms of weight loss and intrahepatic fat. Weight loss responders showed higher methylation in four differentially methylated regions (DMR) and lower methylation in another four DMR compared to non-responders – those who regained lost weight (Supplemental Table 3) (Keller et al., 2020). Furthermore, responders to both weight loss and intrahepatic fat loss showed a smaller increase in methylation age (mAge) than non-responders. mAge proposes to predict age based on the level of methylation at specific sites (Yaskolka Meir et al., 2021a). The only difference in methylation with interventions occurred in cg14335324 of *A2MP1*. Groups that received a low-fat diet showed an increase in methylation, while those receiving MedDiet had a decrease in methylation at this site. It is suggested that the reduced methylation resulting from MedDiet is a consequence of its anti-inflammatory/antioxidant properties (Yaskolka Meir et al., 2021b).

### **Summary on nutrition and epigenetic alterations**

30% dietary restriction may promote DNA or histone methylation. There is a potential impact of dietary fat content, with olive oil showing epigenetic mechanisms related to the prevention of cancer development and progression. However, in humans is far from clear whether the reported changes in DNA/histone methylation are sufficient to regulate gene expression to impact phenotype and age-related outcomes.

Although epigenetic mechanisms are considered one of the best predictors of chronological age and age-related phenotypes, some variability across studies arises from individual variation in biological age, differences between sexes and sample sizes, and cell type-derived DNA (Bell et al., 2019).

### **Loss of proteostasis**

Proteostasis (protein homeostasis) is regulated by several cellular systems that ensure proteins are properly synthesized, folded, and sub compartmentalized (Koga et al., 2011). When any of these systems fail, there is an accumulation of damaging components, contributing to cellular aging and underlying age-related diseases, such as neurodegenerative diseases (i.e. Alzheimer disease and Parkinson disease), metabolic disorders, and systemic disorders, such as amyloidosis (Koga et al., 2011; López-Otín et al., 2013). The main systems involved in protein quality control are the molecular chaperones (or heat shock proteins - HSP) and the proteolytic systems ubiquitin/proteasome (UPS) and autophagic-lysosomal, especially the macroautophagy (MA) and the chaperone-mediated autophagy (CMA) (Koga

et al., 2011). It is noteworthy that MA also targets entire organelles and non-protein macromolecules (López-Otín et al., 2023).

## **Loss of proteostasis and dietary restrictions**

### ***Preclinical models***

DR ensures adequate proteostasis in situations of proteotoxicity (a hallmark of neurodegeneration), primarily through regulation of autophagy and chaperone-mediated folding. In the brain of mice with neurodegeneration, 48-hour intermittent fasting resulted in increased macroautophagy activity (MA). This was a result of increased signaling and expression of the LC3-phosphatidylethanolamine conjugate (LC3II) and reduced MA cargo protein p62 (also known as SQSTM 1) (Ntsapi and Loos, 2021). There was also an increase in lysosome-associated membrane protein type 2A (LAMP2A), suggesting an additional impact on chaperone-mediated autophagy activity (CMA) (Ntsapi and Loos, 2021).

An aged-related reduction was observed in the chaperone family and in proteasome activity, which could be mitigated by promoting 40% CR or intermittent fasting (Bonelli et al., 2008; Colotti et al., 2005). Even in a high-fat diet context (42-43% fat), both CR and intermittent fasting were able to improve markers of autophagy, with increases in 1) mRNA level of the Hsp70 and Hsc70, 2) protein expression of LAMP2A (CMA activity) (Schloesser et al., 2015), 3) LC3I protein, and 4) *Map1 lc3 b* transcript (Chaudhary et al., 2022).

In the skeletal muscle of aged rats, CR suppressed the increase in 26S proteasomes, proteasome-associated proteins, and p97 and its cofactor p47 (Altun et al., 2010). It is suggested that CR could counteract proteasome accumulation and accelerated proteolysis (Altun et al., 2010). Similar results were found in middle-aged rats, in which 40% CR was able to ameliorate changes in FOXO3a (triggers protein breakdown), ubiquitinated protein content, and total proteasome, which are commonly altered in atrophied muscles (Chen et al., 2019).

### ***Human trials***

By applying an early time-restricted feeding (eTRF), in which the last meal of the day happens at 2 p.m. and is followed by an 18-hour fast, there was an increase in macroautophagy activity through increased expression of the LC3A gene. Such an effect was demonstrated in adults with pre-obesity or obesity in a short-time adherence (four days) (Jamshed et al., 2019). There is little evidence of improvements in muscle autophagy in

humans after fasting. In adult women with overweight/obesity, reductions in mRNA levels of *Beclin1*, *Sqstm1*, and *Lamp2* were observed after 8 weeks of intermittent fasting, but only after one fed day (Chaudhary et al., 2022).

## **Loss of proteostasis and dietary patterns**

### ***Preclinical models***

It is suggested that a ketogenic diet (KD) could mimic the effect of CR by upregulating autophagy in the liver of mice (Liśkiewicz et al., 2021; Ochaba et al., 2019). Interestingly, this effect seems to be more pronounced when KD is composed mainly of plant-based fats rather than animal fats (which are rich in SFA) (Liśkiewicz et al., 2021). The improvement in autophagy was demonstrated by higher levels of LC3II and Lc3b mRNA, and lower p62 as early as 48h after the onset of KD. Improvements in autophagy were primarily mediated by downregulation of mTORC1 activity (Liśkiewicz et al., 2021; Ochaba et al., 2019), p53, and FOXO3, and by upregulation of AMPK (Liśkiewicz et al., 2021).

### ***Human trials***

Greater adherence to a daily MedDiet supplemented with 30g of almonds increased the expression of the autophagy-related genes ATG7 and ATG12 in the visceral white adipose tissue of adult women with obesity. It is suggested that the MedDiet could activate autophagy mechanisms due to the presence of polyphenols, such as resveratrol from wine and oleocanthal from extra-virgin olive oil (Osorio-Conles et al., 2022).

## **Summary on nutrition and loss of proteostasis**

CR (30-40%) and intermittent fasting are the most evident dietary interventions regulating mechanisms to ensure adequate protein homeostasis, mainly through the induction of autophagy. The results suggest both strategies as promising interventions to maintain proteostasis in a general context of aging but, more specifically, in neurodegenerative diseases. The potential benefit arises from restricting protein intake, which regulates the UPS pathway in muscle, and adhering to a MedDiet or KD based on plant-based fats. Regarding the last two, the mechanism involves the upregulation of autophagy.

## **Deregulated nutrient-sensing**

Nutrient-sensing pathways are conserved aging control mechanisms that can be modulated. On the one hand, there are the anabolic pathways “insulin and insulin-like growth factor 1” (IIS) and the mTOR complexes, which respond to glucose and amino acids, and on the other hand, the AMP-activated protein kinase (AMPK) and the sirtuins, which senses nutrient scarcity and catabolism by detecting high levels of AMP and NAD<sup>+</sup>, respectively (López-Otín et al., 2013). Downregulation of IIS and mTOR pathways and the upregulation of AMPK and SIRT1 have been associated with increased longevity.

## **Deregulated nutrient-sensing and dietary restrictions**

### ***Preclinical models***

Restricting the diet of *C. elegans* strains results in extended lifespan. It is suggested that this occurs through the upregulation of AMPK, which in turn upregulates the transcription factors DAF-16/FOXO (Greer et al., 2007) or PHA-4/FOXA (Singh et al., 2016). In rodents, fasting and CR can increase the protein levels of SIRT1 in the brain and its gene expression in skeletal muscle, counteracting the effect of age in these tissues (Gräff et al., 2013; Myers et al., 2021; Quintas et al., 2012). A CR of 20% seems sufficient to preserve SIRT1 in rodent hippocampus (Quintas et al., 2012), resulting in reduced local inflammation (Quintas et al., 2012) and senescence (Gräff et al., 2013). This scenario highlights the responsiveness of the hippocampus to CR and the potential protective role of such a regimen against neurodegeneration (Quintas et al., 2012).

In addition, CR and fasting can downregulate the mTOR pathway, in special the pro-aging complex 1 (mTORC1) (Solon-Biet et al., 2019, 2014). Once downregulated, mTORC1 activates PPAR $\alpha$  in the liver, stimulating ketogenesis. Proper ketogenesis is essential to ensure energy sources for peripheral tissues and has been shown to be negatively affected by aging (Sengupta et al., 2010). Proteins, but especially branched-chain amino acids (BCAA), have a critical influence on mTORC1 activation. Thus, reducing the “protein: carbohydrate” ratio or BCAA intake has been linked to increased lifespan and metabolic health in mice (Richardson et al., 2021; Solon-Biet et al., 2019, 2014).

### ***Human studies***

Increased protein levels of SIRT1 have been reported in cells incubated with serum from adults submitted to a 21-day alternate fast (FEAST study) and in those at 25% CR (CALERIE study). However, the greatest benefits seem to be related to fasting. Although CR

also resulted in increased expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- $\alpha$ ), only cells cultured with the serum of those who fasted showed increased survival (Allard et al., 2008). Furthermore, it was previously demonstrated that the alternate-day fasting can also increase SIRT1 gene expression in skeletal muscle (Heilbronn et al., 2005).

## **Deregulated nutrient-sensing and dietary patterns**

### ***Preclinical models***

The administration of  $\beta$ -hydroxybutyrate ( $\beta$ OHB) at a concentration of 4.2% in the drinking water of mice resulted in better metabolic indexes, with higher energy expenditure, reduced food intake (and consequent lower body weight), and better insulin sensitivity. Furthermore, it was observed better object recognition memory.  $\beta$ OHB is one of the major ketone bodies that can be generated from a ketogenic diet. The molecular mechanisms underlying the association between ketone bodies and improvements in healthspan include AMPK, TOR, and ketogenic pathways (Fan et al., 2021).

### ***Human studies***

A recent study with adults and old adults participants of the CORDIOPREV study (CORonary Diet Intervention with Olive oil and cardiovascular PREvention study) showed that some nutrient-sensing pathways are regulated by microRNAs (miRNAs), resulting in different responses depending on the dietary pattern. Accordingly, lower circulating levels of miR-29a, miR-28-3p and miR-126, and higher levels of miR-150 at baseline increased the risk of developing type 2 diabetes mellitus (T2DM) when consuming a MedDiet. Among those consuming a low-fat, high-complex carbohydrate diet (LFHCC diet), this risk was greatest when baseline plasma levels of miR-145 were low. These miRNAs are involved in the regulation of FOXO, PI3K-AKT, and mTOR pathways (Jimenez-Lucena et al., 2021).

## **Summary notes on nutrition and deregulated nutrient-sensing**

Both CR and fasting can extend lifespan across different species by upregulating SIRT1 (Sir2 homolog) and AMPK (SNF1 homolog) or downregulating mTORC1. The effect on mTORC1 can also be achieved by restricting total protein or BCAA. In humans, CR/fasting upregulates SIRT1; however, it is far from known whether such regulation occurs to a sufficient extent to prolong lifespan and whether miRNAs can affect the response.

## **Mitochondrial dysfunction**

Mitochondrial function declines with aging, as does the efficiency of the respiratory chain, resulting in lower ATP generation, greater electron leakage, and increased ROS production (Bratic and Larsson, 2013; López-Otín et al., 2023). Increased ROS works as a stress-triggered survival signal that activates compensatory homeostatic responses essential for cellular homeostasis. Therefore, mild mitochondrial dysfunction has been considered beneficial for lifespan due to a hormetic response (mitohormesis). However, after a certain point, there is a disruption of homeostasis and consequent increase in inflammation and cell death (López-Otín et al., 2023, 2013).

## **Mitochondrial dysfunction and dietary restrictions**

### ***Preclinical models***

Promoting an axenic dietary restriction in *C. elegans* or 40% DR in rodents leads to improvements in mitochondrial function and morphology (Cai et al., 2017; Faitg et al., 2019; Jang et al., 2012), faster turnover (Miwa et al., 2008), increased activity, and attenuates levels of oxidative damage (Jang et al., 2012). However, it is not well elucidate how improving mitochondrial dysfunction could extend lifespan. Current evidence suggests that increased longevity does not require the mitochondrial unfolded protein response (UPR<sub>mt</sub>) (Cai et al., 2017; Deepa et al., 2018a; Mulvey et al., 2017) and is independent of complex IV activity of the mitochondrial electron transport chain (cytochrome *c* oxidase) (Deepa et al., 2018a).

Some caution is needed when interpreting or extrapolating the findings. First, it is worth noting that most of the aforementioned evidence in rodents is based on studies with C57BL/6 mice (Deepa et al., 2018a; Jang et al., 2012; Lettieri-Barbato et al., 2018; Miwa et al., 2008). However, the genetic background may influence the mitochondrial response. While 40% DR did not alter hepatic mitochondrial respiratory capacity in the strain TejJ89, in the TejJ114 strain it was significantly reduced. Opposite results have also been reported, with greater hepatic mitochondrial dysfunction in the TejJ114 strain after food restriction (Mulvey et al., 2017). Second, the mitochondrial response seems to be tissue-specific, with the most significant positive effects seen in the liver and skeletal muscle (Faitg et al., 2019; Jang et al., 2012; Lettieri-Barbato et al., 2018; Miwa et al., 2008), and inconsistent results in the brain (Miwa et al., 2008), cardiac, and adipose tissues (Deepa et al., 2018a). Even in the same tissue, different degrees of response have been reported. In muscle skeletal muscle of rats, it is

suggested a greater impact of DR on oxidative fibers than on glycolytic ones (Faitg et al., 2019).

### ***Human studies***

In adult men and women with obesity, a CR intervention for weight loss resulted in improvements in mitochondrial function, although in men this only happened among those with insulin resistance (Parra et al., 2003, 2005). Regarding nutritional status, the results may be sex-dependent, as among females there was no difference in mitochondrial function according to the presence of obesity (Parra et al., 2003), whether in males, those with obesity had a lower and slower maximum oxidation rate than eutrophic ones (Parra et al., 2005).

On the other hand, in a small sample of young men ( $23.6 \pm 1.0$  years old), prolonged fasting (60h) resulted in mitochondrial dysfunction, and this was positively correlated with bigger lipid droplets (LD) and insulin resistance. These correlations were fully explained by PLIN5 redistribution. PLIN5 is a member of the perilipin LD coat proteins that participates in the oxidative lipolysis of the LD. Thus, fasting may result in the accumulation of myocellular fat through redistribution of PLIN5 (Gemink et al., 2016).

### **Mitochondrial dysfunction and dietary patterns**

#### ***Preclinical models***

In mouse models of mitochondria dysfunction, the ketogenic diet (KD) increased mitochondrial content and its biogenesis in the brain (Lauritzen et al., 2016) and muscle (Ahola-Erkkilä et al., 2010). This high-fat regimen was also associated with improved antioxidant capacity in the hippocampus (Jarrett et al., 2008; Lauritzen et al., 2016).

However, with the KD, mitochondrial distribution and intracellular transport are disturbed, which can affect the proper functioning of neurons and increase the risk of neurodegeneration. Indeed, among mice with a mutation for the mitochondrial DNA repair enzyme, KD accelerated hippocampal atrophy, enhanced neurodegeneration, and reactive astrogliosis (linked to neuroinflammation) (Lauritzen et al., 2016). In addition, in wild-type mice, KD increased the hepatic lipid pool, which is associated with greater inflammation and fibrosis (Ahola-Erkkilä et al., 2010). Thus, greater mitochondrial biogenesis does not necessarily reflect tissue improvements, requiring that other mitochondrial markers and clinical outcomes be considered. In general, the studies are still few, vary in methodology and some strategies have included a diet rich in *trans* fatty acids (Supplementary Table 6).

### ***Human trials***

A short-term (6 days) KD in 10 overweight adults aged  $58.2 \pm 2.8$  years resulted in hepatic mitochondrial changes. Alterations in hepatic mitochondrial fluxes have been demonstrated by decreased glucose and lactate production and by increased hydrolysis of triacylglycerol to generate Acetyl-coA through  $\beta$ -oxidation. Thus, as mitochondrial Acetyl-CoA is shunted towards ketogenesis (increased production of  $\beta$ -Hydroxybutyric acid), the hepatic mitochondrial redox state has increased by 2.7-fold ( $[\beta\text{-OHB}]/[\text{AcAc}]$  ratio). As consequence, intrahepatic triglycerides synthesis and hepatic insulin resistance decreased, although there was an increase in circulating non-esterified fatty acids (Luukkonen et al., 2020).

### **Summary on nutrition and mitochondrial dysfunction**

CR shows to improve mitochondrial function, biogenesis and morphology in different species, including humans. Although this has been associated with an extended lifespan in worms and rodents, the mechanisms underlying this relationship are not well established and there is no evidence in humans. Furthermore, most positive results arise from a specific mouse model and are most clearly demonstrated in the liver and skeletal muscle, suggesting a tissue-dependent response. A KD is proposed to promote mitochondrial adaptations and increase their biogenesis and antioxidant capacity; however, a potential increased risk of neurodegeneration needs to be further explored.

### **Cellular senescence**

Diploid cells exhibit a biological clock, known as replicative senescence, in which the progressive shortening of telomeres limits the number of cell divisions until growth arrest (Calcinotto et al., 2019). Senescence can also be a consequence of non-telomeric DNA damage, oxidative stress, endoplasmic reticulum stress, interferon-related responses, systemic pro-inflammatory state, or a result of external stressors such as chemotherapy (Calcinotto et al., 2019; López-Otín et al., 2013). Although cellular senescence is a beneficial compensatory response against the proliferation of damaged cells, senescent cells can accumulate leading to functional tissue deterioration, accelerating aging (Calcinotto et al., 2019; López-Otín et al., 2013) and underlying multiple non-proliferative diseases including diabetes, atherosclerosis, and Alzheimer's disease (López-Otín et al., 2023)

## **Cellular senescence and dietary restriction**

### ***Preclinical models***

Restricting the diet by 30% to 40% reduces senescence markers and the senescence-associated secretory phenotype (SASP) in the heart (Shinmura et al., 2011), kidney (Wang et al., 2018), and colon (Fontana et al., 2018a) of rodents. Such reductions were demonstrated mainly by attenuation in senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) accumulation and by the reduction of p16 gene expression and protein levels. These changes were associated with lower mortality and cardiac functional decline (Shinmura et al., 2011) and with improvements in kidney function (Wang et al., 2018). The reduced senescence occurred both in short-term (3 months) (Fontana et al., 2018a) and long-term (22 months) interventions (Shinmura et al., 2011) and was more evident when greater restriction (40%) (Fontana et al., 2018a). It is suggested that CR could delay senescence by alleviating oxidative damage through increased autophagic flux (Shinmura et al., 2011). In another preclinical model (zebrafish), however, DR had no impact on SA- $\beta$ -gal accumulation and even shortened telomeres in the brain of young animals, increasing the risk of brain senescence (Arslan-Ergul et al., 2016).

### ***Human trials***

CR was also associated with reduced SASP in older adults ( $61.7 \pm 8.4$  years old) at 30% CR for an average of 10 years. Compared to age-matched sedentary controls, the individuals in CR had lower p16 and lower concentrations of the pro-inflammatory cytokine IL-6 in the colon. This result suggests that the mild senescence phenotype may be mediated by a lower inflammatory profile (Fontana et al., 2018a).

## **Cellular senescence and dietary patterns**

### ***Preclinical models***

Our literature search found no studies on the effect of dietary patterns on cellular senescence in preclinical models.

### ***Human trials***

There is some evidence suggesting a delay in senescence with a MedDiet. In older adults, a short-time adherence to this dietary pattern (~1 month) resulted in a lower proportion of endothelial cells with shorter telomeres, indicative of less senescence. Such an effect was demonstrated through the reduction of ROS production and apoptosis (Marin et al., 2012).

Furthermore, it was recently shown in a small sample of older adults that the long-term adherence (1 year) to a MedDiet was able to alter the expression of several microRNAs (miRNAs), particularly when the diet was enriched with nuts (Mantilla-Escalante et al., 2021). Genes targeted as a result of upregulation of miRNAs after a MedDiet + Nuts included those encoding the tumor suppressors p53 (*TP53*) and PTEN (*PTEN*), the cyclin and cyclin-dependent kinases – which control cell division (*CDK1*, *CCND1*), and pro-inflammatory markers (*MAPK1*). All these genes participate in the complex network of cellular senescence (Mantilla-Escalante et al., 2021).

### **Summary on nutrition and cellular senescence**

The accumulation of senescent cells can be slowed by promoting CR/DR or adhering to a nut enriched MedDiet. A CR/DR of 30% to 40% reduces senescence markers and SASP markers in various rodent and human tissues. Reduced senescence occurs through the up-regulation of members of the sirtuin family and alleviation of oxidative damage and pro-inflammatory profile. In addition, long-term intake of a MedDiet upregulates several miRNAs, which target genes involved in cellular senescence.

### **Stem cell exhaustion**

Stem and progenitor cells are attracted to injured tissues sites by “alarm signals” such as pro-inflammatory cytokines, ensuring a self-repair mechanism (Mansilla et al., 2011). These cells proliferate, migrate, and accumulate in the damaged sites. However, in the long term, the response to DNA damage and replicative stress can lead to the permanent exhaustion of stem and progenitor cells. In this scenario, tissue renewal capacity is compromised, contributing to the development of diseases and accelerating aging (Mansilla et al., 2011; Ruzankina and Brown, 2007).

### **Stem cell exhaustion and dietary restrictions**

#### ***Preclinical models***

With aging, there is a natural decline in stem cell function (Cerletti et al., 2012), which can be counteracted in mice by promoting 30-40% CR/DR. In muscle, dietary restriction resulted in increased frequencies of Pax7-expressing satellite cells, the total yield of satellite cells (Cerletti et al., 2012), and oscillatory expression of genes involved in autophagy. This ensures the recycling of damaged components (Solanas et al., 2017). As a consequence, muscle satellite cells from restricted mice exhibit enhanced myogenic function and a higher fraction of *Sirt1* and *Foxo3a* expression (Cerletti et al., 2012).

Complementary *in vitro* analyzes of muscle cells from restricted mice indicate that CR increases the ability to form satellite cell colonies by modulating mitochondrial mass, function, and biogenesis (Cerletti et al., 2012). Indeed, a restricted regimen rejuvenated the expression of mitochondrial unfolded protein response (UPR<sub>mt</sub>) genes, responsible for mediating quiescence in hematopoietic stem cells (HSCs). Maintenance of quiescence is essential to prevent proliferation-induced DNA damage and functional decline (Tao et al., 2020).

### ***Human trials***

Our literature search found no studies on the effect of CR or DR on stem cell exhaustion in humans.

## **Stem cell exhaustion and dietary patterns**

### ***Preclinical models***

In addition to aging, the macronutrient content of the diet can also impact stem cells. In mice, a high-fat diet (45% of calories from fat) for 4 weeks resulted in functional impairment of intestinal stem cells. However, walnut supplementation counteracted this negative impact. This was followed by reduced tumorigenesis by 32%, although with no impact on tumor progression (Guan et al., 2018).

## **Summary on nutrition and stem cell exhaustion**

The permanent exhaustion of stem cells hinders the regenerative capacity of tissues, which makes them more prone to some diseases. Overall, there is limited evidence for the impact of dietary strategies on stem cell exhaustion. Some potential benefits arise from CR and the inclusion of nuts in the diet, which have been associated with improvements in stem cell function in skeletal muscle and the gut.

## **Altered intercellular communication**

Aging results in changes in neuroendocrine, neuronal, and hormonal pathways that compromise homeostatic and hermetic regulation (López-Otín et al., 2023). These alterations in intercellular communication are primarily cell-intrinsic (e.g., SASP) and ultimately meta-cellular, including inflammatory reactions (López-Otín et al., 2023). The hallmarks of aging are interconnected and converge to “inflammaging” (Franceschi et al., 2018; López-Otín et al., 2023), a chronic low-grade inflammatory state that occurs during aging (Franceschi et al., 2018). Over time, the inflammatory response becomes dysfunctional, resulting in cellular senescence, disrupted proteolysis, apoptosis, and subsequent tissue dysfunction and degeneration (Evans et al., 2020). In addition, “bystander effects” can happen, leading to “spread” of the aging phenotype from one tissue to another (López-Otín et al., 2013).

## **Altered intercellular communication and dietary restrictions**

### ***Preclinical models***

Both 40% food restriction (Deepa et al., 2018b; Xu et al., 2015) and intermittent fasting (IF) (Singh et al., 2015) result in reduced inflammation in rodents mainly by blocking the NF-κB pathway and its downstream effectors. In the kidneys of aged mice, long-term CR resulted in overexpression of SIGIRR as a consequence of the modulation of nutrient-sense pathways (Xu et al., 2015). SIGIRR can block the toll-like receptor (TLR)/nuclear factor-kappa B (NF-κB) pathway. This was confirmed by the reduced expression of the adaptor molecules MyD88 and its downstream IRAK4 and TRAF6 – recruited by TLRs, and of Phospho-IκBα and phospho-NF-κB p65 – indicators of NF-κB activation (Xu et al., 2015).

Reduced levels of phospho-NF-κB and transcription of several inflammatory cytokines were also observed in the white adipose tissue (WAT) of aged mice submitted to CR. Furthermore, this regimen has been shown to reduce the expression of necroptosis markers in WAT. Necroptosis is a programmed cell death pathway that releases DAMPs, a cellular component that activates the inflammaging inductor, NLRP3 inflammasome (Deepa et al., 2018b).

### ***Human trials***

There were no significant differences in markers of immunosenescence in CD4+ T cells in adult and older people (54.6 ± 15.3 years) in CR for about 10 years when compared to their non-CR counterparts (Tomiyama et al., 2017). However, significant results arise from

another study with a younger population and with other inflammatory markers as outcomes. In adults with an average age of 38 years, 25% CR for 2 years implied greater reductions in circulating T3, TSH (Ravussin et al., 2015), Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), high sensitivity C-reactive protein (hsCRP) (Meydani et al., 2016; Ravussin et al., 2015), and reduced number of white blood cells (WBC), lymphocyte, and monocyte count (Meydani et al., 2016). The WBC count has been considered a marker of systemic inflammation (higher, worse). Of note, this mild CR did not exert any detrimental effect on acquired (specific) immunity (Meydani et al., 2016).

## **Altered intercellular communication and dietary patterns**

### ***Preclinical models***

In mice, the ketogenic diet (KD) induces hepatic production of body  $\beta$ -hydroxybutyrate ( $\beta$ HB) within one week (Goldberg et al., 2017).  $\beta$ HB inhibits the NLRP3 inflammasome-induced IL-1 $\beta$  secretion in neutrophils (Goldberg et al., 2017) and in the brain (Guo et al., 2018; Zhang et al., 2020). KD also inhibits AMPK activation. Therefore, there is a suppression of the release of pro-inflammatory cytokines, impeding the translocation of NF- $\kappa$ B p65 to the nucleus. Once in the nucleus, NF- $\kappa$ B p65 binds to the DNA sequence in the promoter regions of inflammatory genes (Harun-Or-Rashid and Inman, 2018). In addition, the KD regimen has been shown to increase the levels and expression of the anti-inflammatory cytokines IL-4, Arg1 (Harun-Or-Rashid and Inman, 2018) and IL-10 (Zhang et al., 2020).

However, a detrimental effect has already been reported in rats with hypertension. In these animals, 4 weeks of KD with 90% fat resulted in opposite effects, with increased production and phosphorylation of TNF- $\alpha$  and IL-1 $\beta$  in the mesenteric arteries. As a consequence, there was induction of an inflammatory state related to endothelial dysfunction and aggravation of hypertension (Guo et al., 2020).

### ***Human trials***

Overall, dietary patterns consisting mainly of fruits, vegetables, low-fat dairy, and reduced intake of red meat and sugary foods were associated with lower concentrations of inflammatory markers in humans. In a large cohort of older adults from Hong Kong, lower concentrations of hsCRP were associated with greater adherence to the Diet Quality Index-International (DQI-I), the Mediterranean-DASH Intervention for Neurodegenerative Delay

diet (MIND) score, the Okinawan diet score, and the “vegetables-fruits” and the “snacks drinks-milk” dietary patterns (Chan et al., 2019).

In a multicenter RCT, a group of middle-aged adults (mean age 55 years) consumed for 1.5 to 2 years a Healthy Nordic Diet, based in whole grains, fruits (mainly berries) and vegetables, rapeseed oil, fish and poultry, and low-fat dairy, avoiding sugar-sweetened products and red meat (Ulven et al., 2019; Uusitupa et al., 2013). At the end of the intervention, these adults had stable concentrations of IL-1 Ra in contrast to the control group, which ended up with increased levels (Uusitupa et al., 2013). IL-1 Ra is considered a highly sensitive marker of inflammation in obesity. When looking at the food components of the diet, it was observed that IL-1 Ra was associated with higher intake of saturated fatty acids (mainly present in animal products) and lower intake of magnesium (very present in fruits and whole grains) (Uusitupa et al., 2013).

### **Summary on nutrition and altered intercellular communication**

Restricting the diet results in the amelioration of the inflammatory state by suppressing the NF-kB signaling and reducing the release of inflammatory cytokines, including IL-6, TNF- $\alpha$  and IL-1 $\beta$ . Another strategy is the KD, which has been shown to ameliorate inflammation by inhibiting IL-1 $\beta$  induced by the NLRP3 inflammasome, especially in the brain. This evidence, however, is limited to rodents. In humans, the reduction in the concentration of inflammatory markers is more evident when there is greater adherence to dietary patterns composed mainly of plant-based foods, fish, and low-fat dairy products.

### **Conclusions and perspectives**

The hallmarks of aging are interconnected, making it difficult to assess the impact of each nutritional domain on an isolated hallmark. The main results are summarized in Table 1. CR is the flagship of experimental nutritional interventions. However, two main concerns arise from this dietary strategy: first, regarding its applicability in humans, since few people are keen to subject themselves to this regimen for the long term; second, regarding possible side effects, since CR can lead to psychological stress. Another strategy that could mimic CR while avoiding these two concerns is to restrict some key amino acids, such as BCAA or methionine. From this perspective, it is imperative to devise strategies thinking about how to properly evaluate this regimen in humans in the long term; when to start and when (if

necessary) to stop; and which aging biomarkers can really reflect the effectiveness of this dietary strategy.

Less attention has been given to the impact of overall diet on the modulation of mechanisms associated with aging. Most evidence relies on adherence to dietary patterns source of phytochemicals and unsaturated fatty acids, such as plant-based diets and Mediterranean dietary pattern. New insights emerge from the ketogenic diet, but with benefits restricted to specific clinical conditions and in the short term.

Although not included in this narrative review, it is noteworthy that the dietary strategies focused in this study may influence the “new” hallmark of aging, “age-associated dysbiosis” CR is suggested to favor a microbiome related to improvements in healthspan and perhaps to the extension of lifespan (López-Otín et al., 2023). Age-associated dysbiosis is the alteration in the architecture and activity of the bacterial community (microbiome) that has been shown to occur with aging. This new configuration can show specific characteristics that have been associated with age-related conditions, such as frailty, low cognition, depression, and inflammation (Ghosh et al., 2020). However, there are several microbiome aging trajectories and they are influenced by factors other than diet (e.g., ethnicity, geography, etc.) (López-Otín et al., 2023).

In summary, dietary restriction and certain dietary patterns, such as the Mediterranean dietary pattern, are nutritional strategies that can impact aging rates and the development of age-related clinical conditions. However, methodological limitations and the scarcity of investigations in humans, preclude currently the elaboration of more precise dietary recommendations aimed delaying biological aging.

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## **Conflicts of interests**

The authors declare that they do not have any conflicts of interest to disclose.

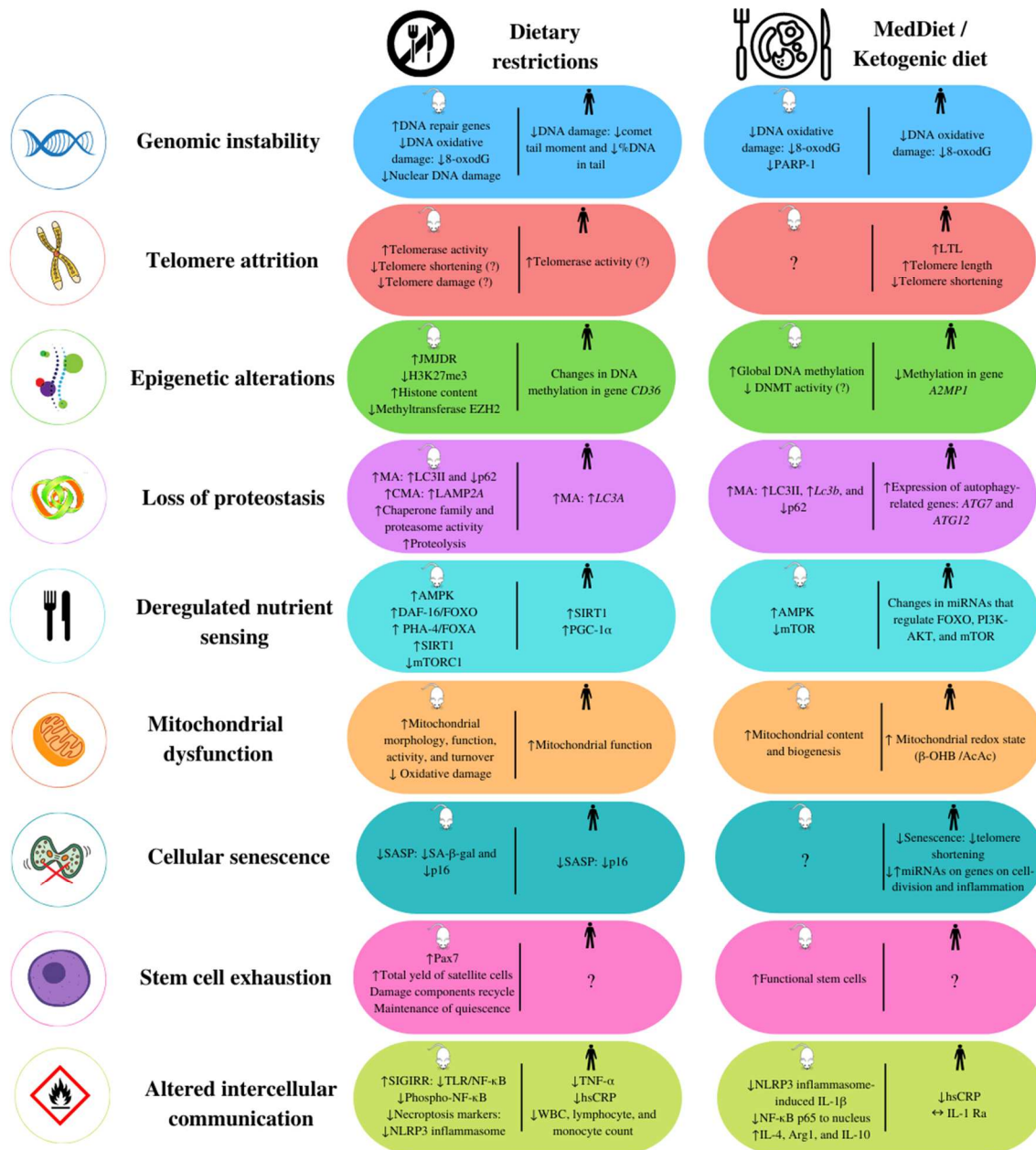
**Table 1** Summary of the findings on the relationship between the three nutritional domains and the cellular hallmarks of aging

Nutritional domain	Hallmark of aging	Dietary approach	Potential Effect	
			Preclinical models	Humans
<b>Dietary restriction</b>	Genomic instability	CR (25% - 55%)	↑	↑
		Fasting	∅	↑
		Protein restriction (40 – 55%)	↑	∅
		Methionine restriction (20%)	↑	∅
	Telomere attrition	CR (40%)	?	?
		Protein restriction	↑	∅
	Epigenetic alterations	CR (30%)	↑	↔
		Protein restriction (33%)	↑	∅
		Methionine restriction (0.12%)	↑	↔
	Loss of proteostasis	CR (40%)	↑	∅
		Intermittent fasting	↑	↑
	Deregulated nutrient-sensing	CR (25% - 40%)	↑	↑*
		Fasting	↑	↑*
		Protein restriction	↑	∅
		BCAA restriction	↑	∅
Mitochondrial dysfunction	CR (40%)	?	↑	
	Prolonged fasting (60h)	∅	↓	
Cellular senescence	CR (30% - 40%)	↑	↑	
Stem cell exhaustion	CR (30% - 40%)	↑	∅	
Altered intercellular communication	CR (25% - 40%)	↑	↑	
	Intermittent fasting	↑	∅	
<b>Dietary patterns</b>	Genomic instability	Mediterranean diet	∅	↑
		Ketogenic diet	↑	∅
	Telomere attrition	Mediterranean diet	∅	↑
		Prudent diet (legumes, nuts, seaweed, fruits, dairy and coffee)	∅	↑
		Red meat, processed meats, and sodas	∅	↓
	Epigenetic alterations	Mediterranean diet	∅	↔
		Diet enriched with olive oil	↑	∅
	Loss of proteostasis	Ketogenic diet	↑	∅
		Mediterranean diet	∅	↑
	Deregulated nutrient-sensing	Mediterranean diet	∅	?
		Low-fat high complex carbohydrate	∅	?
		Ketogenic diet	↑	∅
	Mitochondrial	Ketogenic diet	?	↑

dysfunction			
Cellular senescence	Mediterranean diet	⊗	↑
Stem cell exhaustion	High fat diet	↓	⊗
	Walnuts	↑	⊗
Altered intercelular communication	“Vegetables-fruits”	⊗	↑
	“Snacks drinks-milk”	⊗	↑
	Okinawan diet	⊗	↑
	MIND	⊗	↑
	DQI-I	⊗	↑
	Healthy Nordic diet	⊗	↑
	Ketogenic diet	?	⊗

↑Beneficial modulation; ↓Detrimental modulation; ↔Indifferent; ?Unclear (mixing effects); ⊗Not assessed. DQI-I: Diet Quality Index-International; MIND: The Mediterranean-DASH Intervention for Neurodegenerative Delay diet.

\*Serum of participants submitted to the interventions was used in cell culture



**Figure 1** Summary of the effects in preclinical models and humans of promoting dietary restriction or adhering to specific dietary patterns (Mediterranean diet or Ketogenic diet) on cellular hallmarks of aging. 8-oxodG: 8-hydroxydeoxyguanosine; LTL: leucocytes telomeres; JMJD3: histone demethylase domain-containing protein-3; H3K27me3: tri-methylation histone H3 at lysine 27; MA: macroautophagy activity; CMA: chaperone-mediated autophagy activity; LC3II: LC3-phosphatidylethanolamine conjugate; AMPK: AMP-activated protein kinase; SIRT1: sirtuin 1; mTORC1: mammalian target of rapamycin complex 1; PGC1-α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; miRNAs: microRNAs; β-OHB/AcAc: β-hydroxybutyric acid/Acetyl-CoA; SASP: senescence-associated secretory phenotype; SA-β-gal: senescence-associated β-galactosidase; TLR/NF-κB: toll-like receptor/nuclear factor-kappa B; hsCRP: high sensitivity C-reactive protein; IL: interleucine; TNF-α: Tumor Necrosis Factor-alpha.

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