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The impact of nutrients on the aging rate: A complex interaction of demographic, environmental and genetic factors

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ABSTRACT

Nutrition has a strong influence on the health status of the elderly, with many dietary components associated to either an increased risk of disease or to an improvement of the quality of life and to a delay of age-related pathologies.

A direct effect of a reduced caloric intake on the delay of aging phenotypes is documented in several organisms. The role of nutrients in the regulation of human lifespan is not easy to disentangle, influenced by a complex interaction of nutrition with environmental and genetic factors. The individual genetic background is fundamental for mediating the effects of nutritional components on aging. Classical genetic factors able to influence nutrient metabolism are considered those belonging to insulin/insulin growth factor (INS/IGF-1) signaling, TOR signaling and Sirtuins, but also genes involved in inflammatory/immune response and antioxidant activity can have a major role.

Considering the worldwide increasing interest in nutrition to prevent age related diseases and achieve a healthy aging, in this review we will discuss this complex interaction, in the light of metabolic changes occurring with aging, with the aim of shedding a light on the enormous complexity of the metabolic scenario underlying longevity phenotype.

Contents

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1. Introduction

Aging is an inevitable biological process, characterized by gradual, spontaneous biochemical and physiological changes leading to increased susceptibility to diseases, decreased ability of stress response and loss of independence. The inability of an organism in coping with these changes increases the individual frailty status and may lead to the onset of degenerative age-related diseases, finally decreasing the individual life span. High interest of research is devoted to understand genetic and non genetic factors impacting the aging process and contributing, as such, to the large inter-individual variability in human lifespan.

Among the interventions proposed to slow aging and increase healthy lifespan, promising results came from dietary interventions such as intermittent fasting and protein restriction (Longo et al., 2015). Studies in invertebrates and rodents largely demonstrated the positive influence of caloric or dietary restriction (CR o DR) in extending longevity up to 50%. These interventions were confirmed in genetically mutated organisms with mutations in nutrient and growth signaling pathway, able to slow down age-related diseases including cancer, cardiovascular (CVD) and neurodegenerative diseases (Fontana et al., 2010). A growing interest was recently concentrated on the power of preventing diseases such as cancer or CVD by reducing protein intake: recent evidences demonstrate that a reduction of protein consumption, especially of animal proteins, during middle age followed by an increase from a moderate to high protein consumption in older adults may optimize health span and longevity (Levine et al., 2014). Furthermore, a key role is played by micronutrients (including vitamins and essential minerals such as zinc, copper, selenium), the deficiency of which in aging is strictly related to global impairments of the immune functions, metabolic harmony and antioxidant defense by external noxae with subsequent onset of age-related diseases (Failla, 2003).

The relationship between diet, longevity and human health is complex, considering that nutritional component; affect several physiologic processes, assuming a regulatory role in metabolic pathways crucial for the cell survival such as inflammation or immune function (Santoro et al., 2014). It is also commonly accepted that the complex interactions of multiple polymorphisms play a key role in how individuals may respond to dietary interventions (nutrigenetics) or how some nutrients may affect the gene expressions (nutrigenomic) (Darnton-Hill et al., 2004). Finally, an important modulator of the relationship between diet, longevity and human health is the socio-economic status of individual (Darmon and Drewnowski, 2008).

Aim of this review is to understand how the interaction between nutrients, demographic and genetic/epigenetic factors may influence the aging process and the chance to attain longevity, by regulating crucial processes for human life span (Figs. 1 and 2).

2. Nutrition, health and diseases

Nutrition is the process by which living organisms obtain food and use it for growth, metabolism, and repair. A human diet is composed of macronutrients and micronutrients. *Macronutrients* include proteins (and amino acids, AA), carbohydrates and lipids, thus all dietary components providing our calorie needs. *Micronutrients* include vitamins and essential minerals (zinc, copper, and selenium), supporting biochemical and metabolic activities required for optimal health. Part of nutrition is also the consumption of water and fibers, the last considered not nutrients but having a fundamental importance for some metabolic functions linked to the intestinal absorption of nutrients.

2.1. A brief description of nutrients included in human diet

Among the macronutrients, AAs have constructive functions, but they also represent the substrates in energy metabolism and potent signaling molecules in the regulation of protein metabolism (Wu, 2009). Out of 21 AA, 9 are considered nutritionally essentials in mammals, as they cannot be synthesized in adult humans, and among them leucine is key regulator of protein synthesis (Dillon, 2013). Carbohydrates, are the main source of energy, especially during physical activity. They have plastic function, intervening in the formation of nerve structures, reserve function, as well as informational function, being involved in the metabolism of nucleic acids. After their transformation into glucose, carbohydrates can go through three different metabolic processes: they can be (a) used by cells to produce energy; (b) stored in liver and muscles as glycogen; (c) transformed into fat and deposited as such, when glycogen stores are saturated. The liver operates glycemic regulation: when blood sugar drops, liver releases glucose from hepatocytes, when it rises, liver stores glucose as glycogen; this keeps intact stocks of muscle proteins.

Lipids are important energy reserve for animals and plants (seeds), as they are able to release a large amount of calories per unit mass, considering that the caloric value of a gram of lipids is about double compared to sugars and proteins. Furthermore, they are fundamental components of cellular membranes in all tissues, promoting the intestinal absorption of fat-soluble vitamins and are precursors of compounds with important regulatory functions in the body. Depending on the absence or presence of double bonds, fatty acids are divided into saturated and unsaturated, respectively. Nutritionally interesting are polyunsaturated fatty acids (PUFA), characterized by series of double links conferring to the whole chain a dynamic trend and an increasing fluidity to membranes where they are embedded, in the form of components of phospholipids and glycolipids. The main n-3 PUFAs, contained almost exclusively in fish, are eicosapentaenoic acid (EPA, C20: 5 n-3) and docosahexaenoic acid (DHA, C22: 6 n-3), the last of which most represented in the human body. The main n-6 PUFA, contained primarily in vegetable oils and in the flesh, are represented by the acid γ-linolenic acid (GLA, C18: 3 n-6) and arachidonic acid (AA, C20: 4 n-6). Olive oil is instead rich in monounsaturated fats (MUFA: omega-9 fatty acid, oleic acid), which have been associated with blood pressure and lipid reduction in Mediterranean and other diets (Ferrara et al., 2000; Preedy and Watson, 2015).

When introduced with food, nutrients give their energy by the reactions of the Krebs cycle or Citric Acid cycle (TCA), taking place inside the mitochondria, where in association with the electron transport chain each macronutrient is transformed into the respective intermediates (protein in aa, sugars in glucose then pyruvate, fats into ketones).

Micronutrients are all the nutrients assumed by food not considered energy source, because their function is not directly related to energy production and growth. At cellular level, however, they are essential as cofactors, because they contribute directly or indirectly to the biological activity of antioxidant enzymes (superoxide dismutase, SOD; glutathione peroxidase, GPx; catalase), as well as to mitochondrial energy metabolism and hormonal signaling (Ames et al., 2005). Micronutrients are necessary in small quantities in the organism, normally less than one gram per day, and are divided in vitamins and minerals.

Among minerals, calcium, phosphor, potassium, sodium, chlorine and magnesium are more abundant as nutritional need (gram/day), while zinc, selenium, copper, iron, cobalt, manganese, iodine, fluoride, chrome, vanadium, silicon, are known as trace elements (milligram/day). Minerals are crucial for cellular homeostasis: as an example, zinc (Zn) is required as "second messenger' for the correct functioning of the immune system and antioxidant

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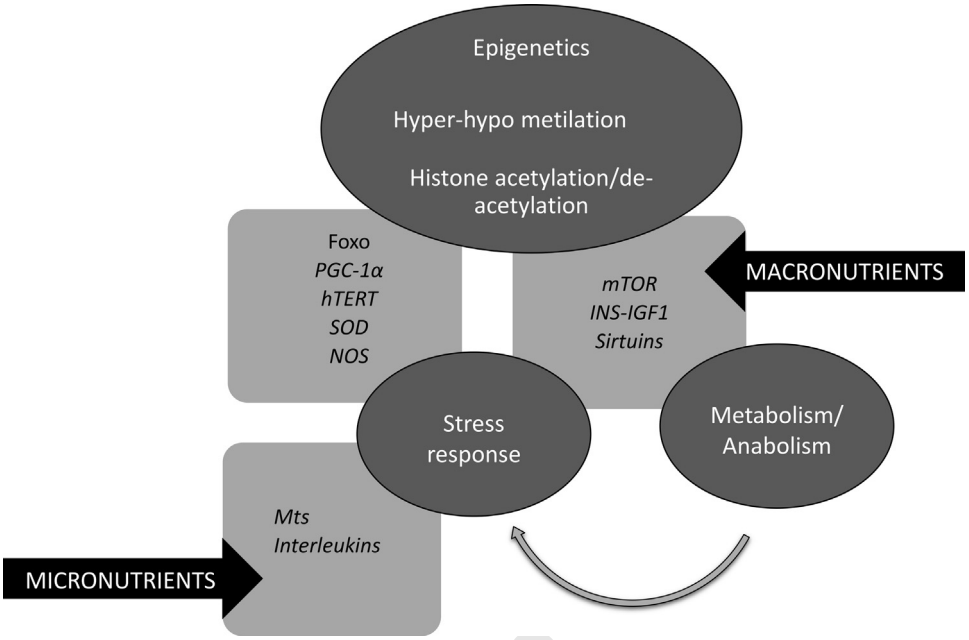

Fig. 1. Genetics and epigenetics of nutrition. The figure shows the main pathways involved in nutrient metabolism. On the left, *mTOR, INS/IGF1 and Sirtuin* pathways are regulated by macronutrient availability. The same pathways are equally involved in stress response and target of epigenetic modifications (hyper- and hypo-methilation). To the right, the other genes target of epigenetic changes, also involved in stress response, are indicated. Finally, the square below reports the genes which products act as antioxidant in stress response and are controlled by micronutrients. The balancing between macro- and micronutrients, as well as between metabolism and stress response, guarantees an optimal cell functioning.

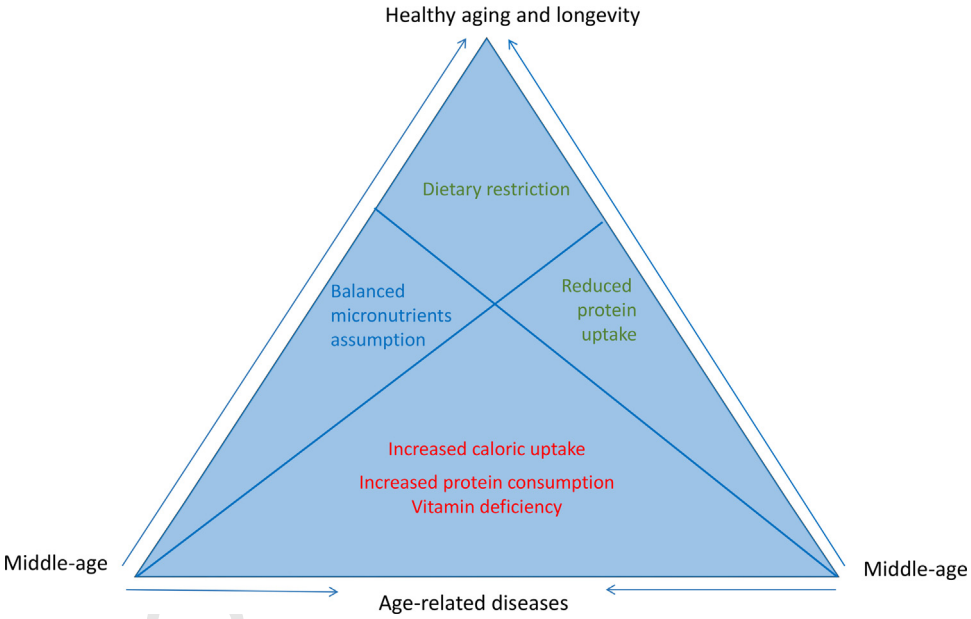

Fig. 2. The road from middle age to longevity influenced by an optimal nutrition. Below, the nutritional habits which may predispose to age-related diseases (increased caloric uptake, increased protein consumption, vitamin deficiency). On the left, the nutritional habits which may help to avoid age-related pathologies (dietary restriction and reduction in protein consumption). On the right, the protective role of micronutrients (vitamin and minerals) on oxidative stress can influence a successful aging and predispose to longevity.

response (Powell, 2000; Chasapis et al., 2012), while selenium, the only element for which incorporation into proteins is genetically encoded, is the constitutive part of selenocysteine and of twenty-five selenoproteins identified so far in the human proteome, all having key roles in antioxidant defense, redox regulation of intracellular signaling, redox homeostasis, and thyroid hormone metabolism (Roman et al., 2014).

Vitamins are organic substances, essential for living organisms, necessarily assumed by diet because the organism is not able to produce them. The only valid operatively classification is their separation into two groups: water-soluble vitamins (B group vitamins, comprising folic acid, niacin or PP vitamin and cyanocobalamin or B12, and vitamin C) and fat-soluble vitamins (vitamin A, E, D and K). The first class of vitamins cannot be stored, thus requiring a daily uptake, while the second one can be assumed with fats and stored into the liver (Joshi, 2015).

The daily requirement for many vitamins (A, D, PP or niacin, folic acid or B9, B1, B2, B6, B12) is available (http://www.lenntech.

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com/recommended-daily-intake.htm); however, vitamin needs can vary depending on the physiological and/or pathological status of the individual: age and sex, but also particular condition as pregnancy, breast feeding or anemia, require an increase of some vitamins, such as folic acid or others (Ladipo, 2000; Bailey et al., 2015; McGuire, 2015).

2.2. Effect of nutrients on health and diseases

A number of observational studies have investigated the association between diet and aging-related health problems, such as cancer risk, diabetes (Everitt et al., 2006), CVD (Kant, 2010), cognition (Allès et al., 2012), and depression (Rahe et al., 2014). It is a common observation that in humans, within western countries, the transition to the modern diet produced an epidemic of nutritionally related diseases including hypertension, atherosclerosis, coronary heart disease, myocardial infarction, congestive heart failure, cerebrovascular accidents, renal insufficiency, renal failure, type 2 diabetes mellitus, metabolic syndrome and obesity (Houston, 2010). In all these cited pathologies, it is the excess of consumption of carbohydrate, lipids and proteins to be responsible of increased caloric uptake, which in turn is responsible of a de-regulation of homeostatic systems. On the contrary, a low-carbohydrate diet reduces body weight and several risk factors for heart disease, as serum levels of leptin, insulin, fasting glucose, and triglycerides (Foster et al., 2003; Aston, 2006; Barclay et al., 2008). Increased lipids or glucose are directly correlated to increased insulin resistance, and in turn determine increase of the blood pressure. A high-fat diet, resulting in the accumulation of white adipose tissue, is associated with increased mortality, as well as increased risk of metabolic disorders (Schrager et al., 2007; Houston, 2010). In particular, dietary saturated fatty acid increase CVD risk by triggering inflammatory response (Mozaffarian et al., 2004, 2006; Upadhyay, 2015); on the contrary, natural unsaturated fatty acids lower blood pressure, improve insulin sensitivity, and reduce the risks of CVD and metabolic syndromes (Summers et al., 2002; Appel et al., 2005). In fact, PUFAs were found to prevent age-related diseases and promote longevity: as an example, arachidonic acid (an omega-6 PUFA) induce apoptosis of cancer cells (Cao et al., 2000) and is able to reduce age-dependent neurodegeneration by increasing the expression of genes crucial for neurogenesis (Das, 2008). However, it was observed that PUFAs levels in the membranes should be maintained low for having benefits for health: this may relate to the fact that some lipids are more resistant to oxidative damage (Hulbert et al., 2005). Consistently, offspring of humans with long lifespan have low levels of PUFAs in membranes of erythrocytes (Puca et al., 2008).

As for proteins, the effect of their intake on human health may depend on dietary source: as demonstrated by follow-up studies on Europeans, a high animal-protein intake positively correlates with a 75% increase in overall mortality and fourfold increase in cancer-related death risk (Levine et al., 2014), whereas high plant-protein intake negatively correlates with the risk (Lin et al., 2011). Furthermore, the consumption of animal protein increases weight gain, whereas intake of plant protein is negatively associated with excess weight and obesity (Lin et al., 2011). Although the mechanisms remain elusive, some authors propose that the lower methionine content in plant proteins respect animal proteins may underlie the beneficial effects of the first (McCarty et al., 2009). Protein turnover rates are differently affected by physiological and disease conditions, which may determine protein accretion or loss at either body or organ levels. In the postprandial period for instance, insulin plays an important anabolic role for muscle (Boirie et al., 2001) while in other situations like inflammation protein synthesis is increased in the liver (Attaix et al., 2005).

As for micronutrients, considering their role as antioxidants, their deficiency can impair biological functions, promoting the development of age-related diseases (Failla, 2003; Bailey et al., 2015). With advancing age, moreover, an increase of oxidative damage to proteins and lipid membranes, particularly in mitochondria, causes a deformation of the structure of enzymes, with a consequent decrease of enzyme activity and binding affinity for their substrates. Deficiency of essential minerals and vitamins can accelerate mitochondrial decay, especially neurons (Ames et al., 2005). It was demonstrated that increased level of substrate by micronutrients restores the speed of the reaction as well as mitochondrial function (Liu et al., 2002). Approximately 20% of bone mass changes can be explained by micronutrients availability: Vitamin D, calcium, as well as a sufficient amount of vitamin K, vitamin A, fluoride, phosphor, and zinc help to improve bone health at later ages (Gennari, 2001). Furthermore, zinc deficiency (genetic or nutritional) as well as imbalance in zinc homeostasis, is associated with age-related diseases, specifically those involving adaptive and innate immune responses, systemic inflammation and impaired antioxidant defense, such as autoimmune and neurological disorders (Fraker and King, 2004; Chasapis et al., 2012; Wong and Ho, 2012). Low levels of vitamin B12 have been associated with memory loss and linked to age-related hearing loss in older adults. On the contrary, large doses of antioxidants can prevent chronic age-related diseases (including CVD, metabolic diseases and neurodegeneration), most of them being attributed to an excessive production of reactive oxygen species during DNA metabolism (Shaw et al., 2014). Among the many examples found in literature, zinc along with vitamins C and E, and the phytochemicals lutein, zeaxanthin and beta-carotene may help prevent or slow the onset of age-related macular degeneration (Anderson and Prior, 2007). Folate, which is related to B12 metabolism in the body, may actually improve hearing, as well as counteract another important factor of decreasing health like dementia (Houston et al., 1999; Araújo et al., 2015). Folate is a critical methyl donor for the synthesis of nucleotides and for the epigenetic control of gene expression via cytosine methylation. It is crucial for preventing genomic instability such as increased incorporation of uracil and DNA base oxidation in the genome, so slowing down such toxic processes.

3. Nutrition and aging

It is known that a healthy lifestyle, which includes a moderate level of physical activity and a balanced diet, may contribute to healthy aging (Dato et al., 2013). However, during the aging process, human physiology changes noticeably. Physiological changes, including for example loss of muscle mass, digestive problems and deterioration of oral health, as well as degradation of sensory functions, may have an adverse effect on dietary composition at old age. Sensory deficits include a decline in sight and peripheral vision, hearing, smell and taste; their loss, neither total nor rapid, results in changed perception of consumed food and beverages. On the other hand, functioning of every nutrition stage, such as ingestion, digestion, absorption, transport, assimilation, and excretion can be deteriorated with aging (Guigoz et al., 1996). Furthermore, frailty and development of co-morbidities may severely influence the attitude to a proper nutrition.

Aging affects dietary habits also in terms of total calorie intake: energy requirements diminish with aging, due to the reduction of activity. However, the supply of proteins (e.g., for preservation of muscle mass), vitamins and minerals (e.g., for bone health) should remain at least the same or preferably slightly enhanced. In consequence, nutrient-dense food choices are recommended for older adults. The calorie need per day of a person over 50 years of age depends on the level of activity, and it differs by gender. For women,

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1600 calories for low level of physical activity, 1800 calories for moderate activity, and 2000–2200 calories for an active lifestyle should be required; for men, 2000 calories, 2200–2400 calories, and 2400–2800 calories, respectively (font: National Institutes of Health, 2005). In the elderly, population-based nutritional surveys show a gradual decline in energy intake, with an imbalance between energy from carbohydrates, which results to increase, and a decrease in energy from fat (de Groot and van Staveren, 2010). The decrease in protein and fat intake in the elderly is associated with mortality, while carbohydrates show a threshold effect on frail elderly patients (Frisoni et al., 1995). Both protein energy wasting and unfavorable dietary regimens leading to fat overload and micronutrient deficiencies can compromise healthy aging.

Protein–energy homeostasis is a major determinant of healthy aging. During the process of aging, although basal rates of protein synthesis and degradation are largely unaffected, the sensitivity of older muscle cells to the anabolic action of essential amino acids is globally lower than in young subjects (Dillon, 2013). The decrease in anabolic sensitivity may depend on several factors, as reduced sensitivity to insulin, reduction in endothelial function and increased oxidative stress (Rasmussen et al., 2006). The impaired response of skeletal muscle to nutrients (Guillet et al., 2004; Cuthbertson et al., 2006), as well as an inadequate nutritional intake (Houston et al., 2008), may finally lead to the age-related decline in muscle mass and function defining sarcopenia, a recognized cause of frailty and disability (Fried et al., 2004).

Vitamin and mineral deficiencies often occur in elderly persons because of a reduction in diet variety and are exacerbated during hospitalization, hyper metabolic states, alcohol use, liver disease, use of diuretics. Apart from copper, iodine and nickel, the amount of which seems to increase with aging, or manganese and cobalt, which do not change with aging, all other micronutrients decrease with aging (Chernoff, 2005). As previously reported, a part from increasing the risk of some age-related pathologies, as neurodegenerative decline, vitamin deficiency contributes to a higher incidence of viral infections and cancer typical of the elderly. In some cases, as for vitamin D, the low uptake with food is exacerbated by the reduced ability to synthesize this vitamin in old people, further aggravated by the lower sunlight exposure (Elmadfa and Meyer, 2008). Vitamin D deficiency was associated with deleterious effects including frailty, decreased physical performance, falls and increased mortality in elderly (Shardell et al., 2009; Zittermann et al., 2009). Moreover, it is known that phosphate homeostasis, together with a bone–kidney endocrine axis, can mediate lifespan and age-related pathologies. Increased body phosphate concentrations due to klotho or fibroblast growth factor-23 deficiency result in the premature onset of aging phenotypes and compromised glucose metabolism (Kuro-o, 2010).

3.1. Dietary interventions able to influence aging

Many studies tried to specify which nutritional components contribute to aging, including early mammalian studies (Maeda et al., 1985; Masoro, 1985, 2005; Yu et al., 1985; Iwasaki et al., 1988a,b; Weindruch et al., 1988; Masoro et al., 1989), and this is currently an active area of investigation. However, the use of experimental organisms to test the effects of nutrients on aging can give controversial results, because such effects may be variable depending on species. In flies, as an example, the ratio of protein and carbohydrate (P:C) is more important for lifespan regulation than individual nutrients (Min and Tatar, 2006; Bruce et al., 2013). Likewise, low P:C diets are beneficial for health and aging in rodents (Solon-Biet et al., 2014).

Along the evolutionary scale, *caloric restriction* (also called dietary restriction, DR, in research papers) is a conservative mechanism able to extend healthy, average, and maximum life span. In mice and rats, a 40% increase in maximum life span can be obtained through life-long DR, while in primates it was demonstrated to delay aging processes and postpone the onset of age-related diseases (Colman et al., 2014).

The molecular mechanisms underlying this effect include a lower rate of tissue oxidative damage, associated with a significantly lower rate of mitochondrial free radical generation in rodent species, as well as a slower accumulation of DNA damage, such as double-strand breaks, which can trigger cellular senescence.

In humans, clinical trials of food restriction in healthy adult subjects, running over 2–15 years, show significant reductions of risk factors for metabolic diseases, as well as an ability in preventing alterations in myocardial and skeletal muscle impairment (Masoro, 2005; Piper and Bartke, 2008; Cox and Mattison, 2009; Barzilai and Bartke, 2009). Evidences to date show that the practice of DR can have the potential to extend the healthy human life span, but there simply is not enough data yet to pin down the effects on life expectancy.

A typical calorie restricted diet contains 25–50% less calories than normal, but maintains essential vitamins and minerals at a nutritionally adequate level, in particular vitamin B3 and its important metabolites, NAD (nicotinammide adenin nucleotide) and NADP (nicotinammide adenin dinucleotide phosphate). However, also a less restricted dietary regimen, such as the "Mediterranean" diet, can have a beneficial effect on the reduction in death rates, including those caused by CVD and cancer (Mitrou et al., 2007). This is a dietary regimen rich of fruits and vegetables, seafood, olive oil, hearty grains, and poor of meat and saturated fat. A high adherence to the traditional Mediterranean diet is associated with low mortality (higher longevity) and reduced risk of developing chronic diseases (Vasto et al., 2014 and references therein). Even short-term adherence (10-days) to a Mediterranean-style diet may benefit aspects of psychological and cardiovascular functioning (Lee et al., 2015). Reports indicate that some dietary components, such as olive oil, antioxidants, N3- and N6-PUFA, polyphenols and flavonoids, mediate the observed anti-aging effects (Chedraui and Pérez-López, 2013).

Many of the characteristics of the traditional Mediterranean diet are shared with other healthy dietary patterns, such as the Okinawan one. This Japanese sub-group of extremely long-lived individuals is among those analysed to find traditional dietary patterns potentially associated with longevity (Beuttner, 2008; Willcox et al., 2014). A reduced risk of chronic diseases is associated with such a dietary regimen, characterized by a higher amount of vegetables and fruit (therefore rich phytonutrient and antioxidants) but reduced in meat, refined grains, saturated fat, sugar, salt, and full-fat dairy products (Willcox et al., 2014). In addition to have a high consumption of plant foods and lower consumption of animal products these populations with an unusually high prevalence of centenarians all tended to be (or had been) very physically active, non-obese and small in stature, suggestive of some degree of calorie restriction.

Dietary intake of centenarians and long-lived populations has been studied from various perspectives, trying to understand whether there are particular diets that may enhance longevity (Shimizu et al., 2003; Willcox et al., 2014). This, however, is difficult to study and verify because of the imprecision in recording food intake, as well it is not practical to monitor food intake over a 100-year lifespan. Furthermore, the vast majority of individuals in the same birth cohort as centenarians, who likely consumed the same local diet, did not survive to such advanced ages. Nonetheless, studies suggest that body mass index and nutritional status of centenarians, as indicated by circulating levels of antioxidant vitamins, vitamin B12, folate, homocysteine and 25(OH) vitamin D, are quite heterogeneous and influenced by region of residency and

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demographic, dietary and lifestyle factors that influence nutritional status in other older adults (Hausman et al., 2011).

As for specific nutrients, studies in model organisms indicate a general negative correlation between the amounts of dietary proteins and lifespan (Buch et al., 2008; Solon-Biet et al., 2014). Few studies addressed the protein needs of frail elderly, and there is insufficient longer-term research with defined health outcomes to establish an optimal protein intake for preservation of lean body mass and body functions (Volkert and Sieber, 2011). However, authors mainly agree that *reducing protein intake* during middle age followed by an increase from a moderate to high protein consumption in old adults may optimize health-span and longevity (an increase of protein intake after 65 years of age can decrease the risk of frailty) (Levine et al., 2014). Furthermore, other dietary components, such as fatty acids, may have a stimulating effect on muscle protein synthesis, as recently demonstrated for long chain polyunsaturated n-3 fatty acids (LcN3-PUFA) in older adults (≥65 years) (Smith et al., 2011). The exact mechanisms responsible for the beneficial effect of LCn-3PUFA on muscle protein metabolism are unknown but one might speculate that they are related to their anti-inflammatory properties. In addition to the effects of overall proteins, many studies have determined the effects of specific dietary AAs on lifespan, by regulation of nutrient-sensing signaling pathways. The most interesting finding is the methionine restriction, able to increase lifespan in *Drosophila* by downregulating TOR (Target of Rapamycin) signaling (Lee et al., 2014). Consistently, methionine restriction extends lifespan in variety of rat strains with different pathological backgrounds, suggesting that methionine deficiency alters the rate of aging and does not predispose to a specific disease (Zimmermann et al., 2003).

In addition to dietary restriction, that limits energy intake from macronutrients, aging and age-related degenerations can be further mitigated by *nutrient supply* including folate, selenium, vitamin B3, vitamin E, vitamin D, and phosphate, and by dietary components such as resveratrol and coenzyme Q from grapes. Longitudinal studies on dietary daily intake in centenarians suggest that a satisfactory content of some micronutrients (zinc, copper, selenium) within the cells maintain unaltered the immune functions, a low grade of inflammation and preserve antioxidant activity (Mocchegiani et al., 2014). However, there is also increasing evidence that vitamins reduce lifespan (Lee et al., 2015). The first observation of a negative effect of micronutrients on aging phenotype came from studies in experimental organisms, in particular in rats, where vitamin C supply reduces the enhanced mitochondrial functions caused by physical exercise (Gomez-Cabrera et al., 2008). The authors associated this effect to a reduced expression of some transcriptional factors required for mitochondrial biogenesis, such as PGC1 (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1), nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (mTFA). In humans, vitamin C and E supplementation decreases oxidative stress but inhibits the beneficial effects of physical exercise on enhanced insulin sensitivity (Ristow et al., 2009). Interesting and comprehensive meta-analyses showed that an "overdose" of vitamins and minerals, respect the recommended daily need, mildly increases human mortality (Lesperance et al., 2002): in particular vitamins having an antioxidant function demonstrated a high positive correlation with mortality (Bjelakovic et al., 2007). Probably the negative effect of antioxidant supplementation may depend on their amount, considering that moderate levels of reactive oxygen species (ROS) have beneficial effect for longevity (Dato et al., 2013), due to their characteristic of cellular signaling molecules, so antioxidant vitamins may seriously reduce this beneficial role of ROS. Overall, evidences indicate that the conventional view that vitamin supply promote health and delay aging should be applied with caution.

On the whole, suggestive evidences in humans and experiments in laboratory organisms indicate that dietary balance among nutrients has bigger effects on aging than individual components (Lee et al., 2008; Skorupa et al., 2008; Solon-Biet et al., 2014). On the contrary, the inability to proper balance energy intake and expenditure with nutrient supply is associated with reduced lifespan in both *Drosophila* (Skorupa et al., 2008) and mice (Solon-Biet et al., 2014). In the last, in particular, caloric restriction achieved by high-protein diets or dietary dilution had no beneficial effects on lifespan, while longevity and health were optimized when proteins were replaced with carbohydrates (Solon-Biet et al., 2014). In *ad-libitum* feeding mice, a low-protein/high-carbohydrate (LPHC) diet increased lifespan and improved metabolic parameters such as insulin, glucose, and blood lipid, obtaining metabolic benefits of CR without a 40% reduction in total caloric intake (Solon-Biet et al., 2014).

3.2. Demography and nutrition: how nutrition changed the male/female ratio

Many changes have occurred in human lifestyle across western countries in the last century. In particular, the cleaner environment, the mass vaccines and the antibiotic therapies have significantly reduced the mortality due to infections, which had been, by far, the most important cause of death for all the human history. This led to a dramatic reduction of infant and juvenile mortality, with more than 90% of people living beyond 65 years of age. Thus, in these societies there has been an unprecedented increase of life expectancy with most of deaths occurring among the elderly population (Passarino et al., 2006). Therefore, typical age related diseases, such as cancer, cardiovascular and neurodegenerative diseases increased their occurrence. Such diseases, in particular cancer and CVD, are significantly influenced by nutrition and especially by the changes in nutrition, which has occurred in western societies. In fact, from the 1950s onward there has been a significant increase of lipids and of proteins, especially from animal source, in the diet of western populations (Levine et al., 2014; Beltrán-Sánchez et al., 2015); for instance, in Italy the consumption of proteins and lipids of animal origin have quadruplicated in the second half of the XX century (data from www.istat.it). These nutrients affect the individual susceptibility to cancers and CVD in the elderly and, then, affect mortality. However, recent studies, have shown that the effects of these nutrients is particularly significant on men, and this may explain the excess of male mortality in 60+ subjects observed from the second half of last century (Beltrán-Sánchez et al., 2015). Indeed, among long-lived subjects, females outnumber males in all the countries. In most of the European countries, the female/male ratio among centenarians is about 4/1. Interestingly, in line with this hypothesis, lower ratios, close to 2/1 or even 1/1, were found in areas where the diet is characterized by lower protein and lipid uptake, such as southern Italy, Sardinia, Okinawa and the Amish population (Mitchell et al., 2001; Passarino et al., 2002; Montesanto et al., 2008; Gavrilova and Gavrilov, 2012; Pes et al., 2015). Consistently, the incidence of CVD in these populations is lower than in the rest of their countries. Thus, the nutrition can affect the demography of modern societies by affecting the female/male ratio in the elderly population segment, which is the most rapidly increasing segment. The very recent dietary tendency with a decrease of meat consumption and a general the increase of vegan habit, may, in the future, decrease CVD diseases, improve life expectancy and decrease the excess of male mortality. As long-lived males are generally in a better shape with respect to long-lived females, if this change will occur this may have important effects on population demography and on the societal challenges.

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4. Genetics and epigenetics of nutrition in aging

Among all the external environmental factors with a direct effect on the genome, nutrition is one of the most influential, due to its ability to affect the transcriptional activity and expression of many genes. The ability to sense and respond to fluctuations in environmental nutrient levels is a key requisite for life: in particular, nutrient scarcity represents a selective pressure that has shaped the evolution of most cellular processes. The integration and coordination of different metabolic pathways, genetic or epigenetic, able to detect intracellular and extracellular levels of sugars, amino acids, lipids, is obtained at the organism level through hormonal signals. During food abundance, nutrient-sensing pathways engage anabolism and storage, whereas scarcity triggers homeostatic mechanisms, such as the mobilization of internal stores through autophagy. Nutrient-sensing pathways are commonly deregulated in human metabolic diseases and currently under study are the exact metabolic mechanisms involved in the nutritional uptake.

4.1. Genetic pathways involved in nutrient metabolism

Nutrient-sensing pathways are not simply to be analysed from a genetic point of view, because they are complex networks, able to sense nutrient-status and regulate metabolic homeostasis by coordinating nutritional stimulus with other cellular information such as growth, development, stress resistance and reproduction. Thus, it was proposed that the complex interactions of multiple polymorphisms in different genes might control the individual responses to dietary interventions (Darnton-Hill et al., 2004).

For understanding the amount of research beyond this issue, it is sufficient to say that 27858 results can be found when submitting the keywords “genetics of nutrition” to PubMed; while 6379 are those found with “human genes and diet” (on 20th November 2015). However; studies converge to a few pathways controlling nutrient metabolism; conserved along the evolutionary scale. In multi-cellular organisms; the requirement for coordination of growth in different tissues creates a need for intercellular communication; which is achieved by diffusible growth factors. In yeast; components of growth-promoting signaling pathway are essentially the Ras proteins; through which glucose availability controls the lifespan. In *Caenorhabditis elegans*; glucose downregulates pro-longevity proteins; such as AMP-activated protein kinase (AMPK); FOXO; and glyoxalase. In cultured mammalian cells; Sirtuin 3 (SIRT3); a NAD-dependent protein deacetylase; mediates the effects of glucose on senescence. Consistently; in humans; the study of nutrient-sensing networks converge on three main pathways: the insulin–insulin growth factor-1 signaling (Ins–Igf1 or IIS); the TOR pathway and Sirtuins. Furthermore; single genes involved in inflammatory response; like interleukine-6 (IL6) and AMPK signaling; even related to Sirtuin pathway; have been hypothesized to mediate the nutrient-aging connection (Kapahi et al., 2010). Actually; all of them resulted to regulate at molecular level the evolutionary conserved anti-aging effects of CR on longevity; integrating extra and intracellular signals from nutrients; growth factors and various stresses.

The TOR pathway is the major way through which essential amino acids induce anabolic response and AA restriction promotes health and long lifespan. Studies in flies, worms, yeast and mice support the notion that the TOR signaling network plays a pivotal role in modulating aging, by sensing both qualitative and quantitative changes in nutrients. TOR belongs to a conserved group of serine/threonine kinases from the phosphatidylinositol kinase-related kinase (PIKK) family. Mammalian target of rapamycin complex one (mTORC1) activity influences mRNA translation, autophagy, transcription, metabolism and cell survival, proliferation, size and growth, in addition to a number of other cellular processes. Its activity is modulated by various growth-signaling factors, like IGF and insulin through Akt, as well as by multiple stresses, such as high temperature, hydrogen peroxide and high salt stress in the yeast (Kapahi et al., 2010). The pathway responds to the energy charge within the cell influenced by the presence of nutrients like glucose and it is especially sensitive to regulation by branched chain amino acid leucine, which stimulatory effect was demonstrated both in vitro and in vivo (Buse and Reid, 1975; Anthony et al., 2002). In humans, association studiesof tagging SNPs (single-nucleotide polymorphisms) in *TORC1*, *TORC2*, *MTOR*, *RPTOR*, *RICTOR* and *RPS6KA1* genes with human longevity (defined as attainment of at least 95 years of age) as well as with health span phenotypes, did not found any correlation with extreme age in Americans from Japanese origin (Morris et al., 2015). Further studies in different populations should be carried out to clarify the potential genetic contribution of *mTOR* pathway genes to human longevity, and clinically relevant aging phenotypes.

As for the Ins–Igf1 pathway (or IIS), it is one of the most conserved pathway linked to aging along the evolution, mediating the effect of glucose on aging itself (van Heemst et al., 2005). Studies in different model organisms have shown that Ins/Igf1 signal transduction plays a key role in the coordination of growth, differentiation and metabolism in response to changing environmental conditions and nutrient availability. In mammals, the pathway is a complex cascade of events, activated by the binding of Insulin, Igf1 or Igf2 to Insulin receptor, and mediated by receptor substrates like IRS1-4, Shc, Grb2, PI-3 and RAS, second messengers like PTEN, and culminating into the activation of transcriptional factors like FOXO through several protein kinases like PDK-1, AKT-1 or ERK1-2. FOXO activation causes a metabolic shift from glucose to lipid oxidation, with concomitant enhancement of cellular stress resistance and protection, suppression of low-grade inflammation and enhanced mitochondrial biogenesis. Common polymorphisms in several of the IIS genes have been associated with longevity across diverse cohorts. Genotype combinations at *IGF-IR* and *PI3KCB* genes were found associated with lower free IGF-I plasma levels and found to be enriched in Italian centenarians (Bonafè et al., 2003). In the Leiden 85-plus study, genetic variants in the *GHRHR*, *GH1*, *IGF-1*, *INS* and *IRS1* loci have a joint effect on old age survival (van Heemst et al., 2005). As well, in Ashkenazi Jewish centenarians and their offspring, higher serum levels of IGF-1 and overrepresentation of heterozygous mutations in the *IGF-1R* gene were found among centenarians (Suh et al., 2008).

Finally, a large body of evidence supports physiological roles of Sirtuins (in particular SIRT1, SIRT3 and SIRT6) in regulating metabolic homeostasis. Especially in mouse models, SIRTs play powerful roles as guardians of mammalian health span, in different disease context (Giblin et al., 2014). SIRT proteins show NAD^+-dependent deacetylase and ADP-ribosyltransferase activities, and regulate several cellular functions via modification of histones, transcription factors, DNA repair proteins, autophagy factors, and other proteins. Considering that SIRT catalytic activity is NAD^+-dependent, and NAD^+ levels rise upon nutrient stress in certain tissues, SIRTs have been proposed to link reduced intake with the pro-longevity response (Giblin et al., 2014). *SIRT*1 regulates gluconeogenesis, fatty acid oxidation, cholesterol efflux, bile acid synthesis, lipogenesis. Furthermore, it is among the genetic factors regulating high fat diet, together with *AMPK*, peroxisome proliferator-activated receptors (*PPARs*), sterol regulatory element-binding protein 1 (*SREBP-1*), carbohydrate-responsive element-binding protein (*ChREBP*), superoxide dismutase 3 (*SOD3*), cysteine-aspartate protease-1 (caspase-1), and others (Lomb et al., 2010; Zadra et al., 2010; Jeon and Osborne, 2012; Dixon et al., 2013; Filhoulaud et al., 2013; Grygiel-Górniak, 2014). SIRT1 is one of the

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best-studied factors mediating the effects of metabolic changes on lifespan in yeast and mammals, by acting as key sensor of nutrient availability and regulating the activity of substrate proteins (Haigis and Guarente, 2006). Increased *SIRT1* expression improves glucose tolerance and insulin sensitivity and extends mouse lifespan (Banks et al., 2008; Pfluger et al., 2008); on the contrary, the SIRT1-knockout in white adipose tissue determine metabolic dysfunctions, such as insulin resistance, increased body weight, and excessive levels of fat in high-fat feeding experimental conditions (Chalkiadaki and Guarente, 2012). Pancreatic β-cell specific overexpression of *SIRT1* promotes insulin secretion and improves glucose tolerance in younger mice (Giblin et al., 2014 and references therein). About the possible mechanisms, underlying the beneficial effect of *SIRT1* expression on organismal survival, it was suggested the up-regulation of genes enhancing mitochondrial function and reducing the excess of energy storage. As for *SIRT3*, its expression was found to reverse age-related functional decline in mice (Brown et al., 2013); in mice and humans, the protein may protect from forms of metabolic dysfunction, including obesity, insulin resistance and liver steatosis. SIRT3 deacetylates metabolic enzyme to promote fatty acid β-oxidation, glucose oxidation and ketogenesis (Giblin et al., 2014). *SIRT3* polymorphisms were found to influence survival: rs11555236, an intronic variant in linkage disequilibrium with a variable number tandem repeat in a putative *SIRT3* enhancer, were found associated with male longevity (Rose et al., 2003; Bellizzi et al., 2005). Individuals homozygous for this variant have increased *SIRT3* expression in peripheral blood mononuclear cells (Albani et al., 2014), thus suggesting a potential beneficial role in important cellular functions.

Finally, SIRT6 plays significant functions in glucose and lipid homeostasis. *SIRT6* global knockout mice typically die from severe hypoglycemia by 4 weeks of age and show aging-like phenotype, as lymphopenia, genomic instability and cardiac pathologies (Mostoslavsky et al., 2006), while its over expression extends median lifespan of male transgenic mice from 10% to 14.5%, together with a preservation of glucose tolerance and insulin sensitivity with age (Kanfi et al., 2012).

During the last decade, the pivotal role played by some micronutrients (zinc, copper and selenium) in maintaining the correct functioning of homeostatic mechanisms (Mocchegiani et al., 2008), prompted the research on regulators of trace elements homeostasis as emerging pathway controlling nutrient uptake. Among these kind of pathway, that of metallothioneins (MT) seem particularly relevant for aging studies, because they are involved in the susceptibility to major geriatric disorders, such as diabetes, osteoporosis, osteoarthritis, dementia, CVD and infections (Mocchegiani et al., 2006a,b, 2014).

MTs regulate intracellular zinc homeostasis, controlling the caption and release of the metal at the occurrence. MT proteins, further, bound also copper (Cu^{2+}), whose most bio available source is meat and the major storage is in the liver (Hartmann et al., 1993). Through the zinc release by nitric oxide and Nrf2 translocation, MTs regulate *Gclc* gene expression, and limit oxidative damage within the cell (Spahl et al., 2003). In chronic stress and inflammation typical of aging, MTs can decrease zinc release, with subsequent low mineral availability to support immune responses (Mocchegiani et al., 2000). With age, it was demonstrated that genes acting as zinc-sensors are altered (Robert and Fulop, 2014): the metal responsive transcription factor1 (*MTF-1*) firstly, and then the subsequent zinc target inflammatory genes, such as *IL-6*,*TNF-a*, *IL-8*, *MCP-1*, *PPARa*, *PPARg* (Mazzatti et al., 2007). Furthermore, deficiency of *MT-1* and *MT-2* genes shortens the lifespan of mouse strains, exhibiting signs of age-related decline, such as weight loss, hunchbacked spines, lacklustre fur and absence of vigour, thus suggesting lifespan shortening and accelerated senescence in absence of *MT* genes (Kadota et al., 2015). In the human genome, MTs are present as a gene family composed by four genes, with the first, *MT1*, harboring at least six isoforms and several pseudogenes. Polymorphisms affecting the zinc–gene network on *MT2A* and *MT1A* genes were found associated with the inflammatory state and longevity. Elderly subjects carriers of the AA genotype for MT2A polymorphism display low zinc bioavailability, chronic inflammation and high risk for atherosclerosis and type 2 diabetes (Giacconi et al., 2005). In *MT1A* gene, the A/C (asparagin/threonin) transition at +647nt position in the coding region was associated with longevity (Cipriano et al., 2006), while the haplotype +647/+1245 was implicated in cardiovascular diseases (Giacconi et al., 2010). Furthermore, in old people, the genetic interaction between polymorphisms at *MT* genes and *IL-6* was suggested to influence the zinc supplementation: the *IL-6*+174G/C locus in particular, in association with *MT1A*+647 A/C gene, determine a plasma zinc deficiency and altered innate immune response (Mocchegiani et al., 2008). These results suggest not only that zinc supplementation may be more or less efficient depending on genes but also that the daily requirement of zinc might be different in elderly harboring a different genetic background.

4.2. Epigenetics of nutrition and aging

Mechanistic studies provide insights into the nutritional influence on epigenetic marks with effects on aging. Aging is associated with global genomic hypo methylation and gene-specific hyper methylation, mainly due to changes in the expression of the *DNMT*s (DNA methyltransferase) (Casillas et al., 2003; Bollati et al., 2009; Huidobro et al., 2013; D'Aquila et al., 2013; Gentilini et al., 2013). In addition, different combinations of histone marks, including acetylation and methylation, that influence chromatin structure, may act in a network to affect longevity (Han and Bunet, 2012; Das and Tyler, 2013). Nutrition and diet have been shown to mediate changes in the above epigenetic mechanisms, and recent studies have eluded that diet, in both its quantity and quality, is linked to aging and cancer incidence and prognosis (Li et al., 2011; Tollefsbol 2014). An interesting example of epigenetic regulation of longevity in response to diet was observed in honeybee (*Apis mellifera*): in genetically identical queen and worker larvae, the intake of royal jelly by the queens influences their morphological and physiological phenotypes, including lifespan. This influence is mediated by DNA methylation as demonstrated by knockdown of the DNMT3 enzyme that results in the development of a queen phenotype from worker-destined female larvae (Kucharski et al., 2008). Foret et al., 2012 observed that the number of differentially methylated genes in larval head was higher than in adult brain and more than 80% of these were found up-methylated in worker larvae, including genes involved in insulin–insulin-like signaling and TOR pathway, thus contributing to the profound divergence in phenotype. More recently, Inoue et al., 2003 demonstrated that mice fed with a diet supplemented with royal jelly for 16 weeks exhibited a more extended average life span with respect to mice with a standard diet.

Outstanding contributions about dietary influences on epigenetics have been proved to occur in utero: gestational period, indeed, has been found being particularly susceptible to nutritional-driven epigenetics remodeling. Moreover, both clinical, experimental studies and epidemiologic data revealed that early life events seemed implicated in influencing later susceptibility to certain chronic diseases and aging process as well (Perera and Herbstman 2011; Szarc vel Szic et al., 2015). Individuals with metabolic syndrome, obesity, type 2 diabetes and CVD may show a lifelong imbalance between energy intake and expenditure due to incorrect epigenetic programing during their early development as a result of placental insufficiency, inadequate maternal nutrition and metabolic disturbances.

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Studies on human populations following famine have suggested that pathologies in later life are dependent on the timing of nutritional insult during pregnancy. Indeed, follow up of the Dutch Hunger Winter cohort showed that CVD were more prevalent in offspring of mothers who were severely undernourished during the first trimester of their pregnancies (1944–1945), as compared to those born from mothers whose pregnancies were more advanced at the time of nutritional insult (Roseboom et al., 2006). In addition, paternal nutrition during the pre-pubertal growth period in children in Överkalix (Sweden), during the nineteenth century was associated with differential risk of early CVD in their grandchildren (Kaati et al., 2002).

Caloric restriction exerts its effects on aging by regulating DNA methylation patterns at specific loci via DNMT1 activation. In particular, genes such as *Ras* and $p16I^{NK4a}$ werefound hypermethylatedand, consequently, down-expressed (Li et al., 2011). Several studies demonstrated that, during the above nutritional regime, the activity of *SIRT1* and *HDAC1* (histone deacetylases) increases as well histone methylation patterns are modified. All these events induce a down-regulation of key genes, such as *p53*, *FOXO*, *Ku70* and *p16INK4a* and up-regulation of *PGC-1α* and *hTERT*. In turn, SIRT1 can deacetylate acetylated DNMT1, thus altering its activity (Peng et al., 2011). As a result, caloric restriction-dependent epigenetic modifications reverse aberrant gene expression during this nutritional regime, contributing to aging delay and lifespan extension. As an example, fetal lung fibroblasts, cultured in presence of low glucose levels, exhibited an extended lifespan and cancer inhibition: in particular, a repression of *p16INK4a* and an activation of *hTERT* was found associated to longevity, as emerged by an extension of Hayflick limit of cells, meanwhile opposite effects were observed in precancerous cells (Li et al., 2011).

Many natural dietary agents, including polyphenol resveratrol, have been proposed to promote healthy aging and to increase lifespan through the alteration of the levels of S-adenosylmethionine (the methyl donor for methylation reactions), *S*-adenosylhomocysteine (an inhibitor of methyltransferases), and the activation of *SIRT1* activity, mimicking caloric restriction (Fernández and Fraga, 2011; Vaiserman & Pasyukova 2012). Similarly, folate, vitamin B-12, methionine, choline, and betaine can affect DNA methylation and histone methylation by altering 1-carbon metabolism. Animal studies also suggest that dietary folate during the post weaning period may modify disease susceptibility in later life. Kotsopoulos and collaborators reported that a low-folate diet provided from the post weaning period to puberty increased genomic DNA methylation by 34–48% ($P < 0.04$) in rat liver that persisted into adulthood (Kotsopoulos et al., 2008). Substances naturally occurring in some foods, such as butyrate, diallyldisulphide (DADS) and sulphorane (SFN), exert their effective action on aging primarily by binding HDACs and inhibiting their activity, thus de-repressing epigenetically silenced genes such as p21 and Bax to promote cell-cycle arrest and/or apoptosis (Dashwood & Ho, 2008). Moreover, several studies have eluded that diet, in both its quantity and quality, is linked to aging and cancer incidence and prognosis. Genistein, a phytoestrogen in soybean, analog to estradiol, (−)-epigallocatechin- 3-gallate (EGCG) from green tea and some isothiocyanates from plant foods inhibit growth and proliferation of cancer cells and exert protective effects on aging. In vitro cell culture studies demonstrated that these components, by reducing DNA hypermethylation through their DNA methyltransferase inhibition properties, up-regulate the expression of key oncogenic genes, such as *p16INK4a*, *p21*, *RARb* (Retinoic Acid Receptor beta) and *MGMT* (*O*-6-methylguanine-DNA methyltransferase). What is more, the above components interfere with enzymatic activity of class I–IV *HDACs*, histone acetyl transferases (*HATs*), and class III *HDAC* Sirtuins (*SIRTs*), which modulate inflammatory responses and immunological senescence. A flavones-rich diet was found associated to a low risk of CVD: in particular, the promoter of several genes involved in the pathogenesis of atherosclerosis, such as extracellular superoxide dismutase (*SOD*), hormone receptors endothelial and inducible nitric oxide synthase (*iNOS* and *eNOS*), 15-lipoxygenase (*LOX*), fibroblast growth factor (*FGF*) 2 was demonstrated to be hyper- and hypo methylated (Pandey and Rizvi, 2009).

5. Final considerations

Oldest old are the fastest growing segment of the population: it has been estimated that the proportion of elderly persons (≥60 years) in the global population will reach 32% in 2050 (United Nations, World Population Prospect). Thus, maintaining health and well-being in aging populations has become a major public health challenge. According to the multidimensional model proposed by Rowe and Kahn in 1997, "healthy aging" should depend by a combination of a low risk of disease and disease-related disability, high levels of mental and physical health, and active engagement with life (Rowe and Kahn, 1997). Furthermore, the heterogeneity of the longevity phenotype is due to the influence of genetic and environmental components (Montesanto et al., 2012), with genes having an impact of 25% in the determination of human lifespan (Herskind et al., 1996). Therefore, to understand the influence of modifiable lifestyle factors on the achievement of health and longevity has become a hot topic in gerontological research. Among the most important modifiable factors that may have an impact on healthy aging, diet is prominent. Both lifespan and health span are influenced by nutrition, considering that nutrients and their metabolites control energy balance, enzymatic activities, and genome stability throughout the lifecycle. Aging is a target of dietary intervention, as demonstrated by the robust association of dietary restriction with increased lifespan and reduction of age-associated decline across a wide range of species. In humans, dietary interventions mimicking chronic dietary restriction (periodic fasting mimicking diets, protein restriction, etc.) have been proposed to slow aging (Longo et al., 2015), as well as it is known that a diet rich in antioxidant may help in contrasting age-related oxidative burden.

However, the relationship between nutrition, health and aging is still not fully understood, as well as it is highly debated the advantage of vitamin supplementation on health. At our knowledge, three cohort studies investigated a posteriori (that means empirically derived) dietary uptake and aging, the Melbourne Collaborative Cohort (Akbaraly et al., 2013), the Whitehall II Cohort studies (Hodge et al., 2014) and the French SU.VI.MAX (SUpplémentation en VitaminesetMinérauxAntioXydants) study (Assmann et al., 2015). Overall, they confirmed the correlation between the "fruit" pattern (positively) and the "meat/fatty foods" pattern (inversely) with specific parameters defining "healthy or successful aging". Furthermore, the study by Assmann on the French population confirmed the inverse association between a high-energy intake (defined as being in the highest tertile; i.e., consumption of ≥1700 kcal/day) and "successful aging". Samieri et al., 2013 tried to build a kind of nutritional score, called Healthy Eating Index, and correlate it with individual parameters of health and age, but contrasting results were found. Methodological differences, including different definitions of healthy aging (in terms of parameters used and cutoff points), absence of major chronic diseases, age- and sex-differences in the study cohorts, may explain inconsistencies among results.

Probably one pitfall can be the consideration of single food instead of dietary patterns: in practice,foods and nutrients are assumed in a variety of combinations, leading to interactive, cumulative, or confounding effects (Jacobs et al., 2009). The study of food synergy actually has a strong biological base, considering that most

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recent researches indicate that dietary balance among nutrients has bigger effects on aging than individual components (Lee et al., 2008; Skorupa et al., 2008; Solon-Biet et al., 2014). Moreover, considering food synergy may help to take into account the influence of each nutrient on the metabolism of the others. For example, the buffer effect that means the effect of a large intake of a particular nutrient may vary depending on if it is taken in concentrated form or as part of a food matrix (Jacobs et al., 2009). Another aspect of synergy may be nutrients that affect each other's absorption, such as vitamin C, which acts as a pro-oxidant in the presence of iron. Furthermore, the protein/non protein nutrient ratio rather than amount of proteins or calories plays key roles in the regulation of lifespan (Mair et al., 2005; Fanson and Taylor, 2012; Bruce et al., 2013).

The few cited cohort studies underline that, starting from midlife, adherence to a healthy diet that provides micronutrients, fiber, and antioxidants while regulating energy intake may help to promote a healthy aging. Thus, although focusing on individual components of the diet, a whole diet approach, comprising a regulated (not necessarily drastically reduced) energy intake and high dietary quality, should have greater beneficial effect on overall health than single nutrient interventions. Simultaneous changes in a selected range of dietary constituents, in particular those focused on reducing chronic low grade inflammation, can ensure that the subtle effects observed from single nutrients will act in concert to optimize healthy aging.

An integrated approach should be applied also to the investigation of the genetic and epigenetic components mediating nutritional uptake, which may help to elucidate molecular targets and pathways influencing dietary intervention. Genetic factors mediating the effects of nutritional components on aging have been mostly focused on insulin/IGF-1signaling, TOR signaling and Sirtuins, but it does not necessarily mean that these factors are the most important. In particular, considering the fact that all these pathways are equally implicated in stress response, and that stress mediators play key roles in their activation, it is likely that stress response pathway should be investigated in relation to nutrient changes also. This consideration should help to integrate micronutrients in the analysis, considering their role in antioxidant defense. It is probable that their role inside cell metabolism should be read together with the availability of macronutrients. Biological mechanisms including enhanced genomic stability and chromatin remodeling, as well as improved chaperone-mediated protein homeostasis, regulated by epigenetic mechanisms, should be added to the analysis of key signaling pathways in nutrient regulation. Finally yet importantly, the identification of the genetics determinants in protein energy wasting in elderly can constitute a promising perspective for identifying the genotypes at risk of malnutrition and activate early intervention. In particular, whereas current recommendations to prevent nutritional deficiencies target most of the population, inclusion of genomic criteria may indicate subpopulations that may incur differential benefit or risk from generalized recommendations and fortification policies (Stover, 2006).

Q15 Uncited references

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