Nutrients and Pathways Regulate Health

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Definition

Both life span and health span are influenced by genetic, environmental and lifestyle factors. With the genetic influence on human life span estimated to be about 20–25%, epigenetic changes play an important role in modulating individual health status and aging. Thus, a main part of life expectance and healthy aging is determined by dietary habits and nutritional factors. Excessive or restricted food consumption have direct effects on health status. Moreover, some dietary interventions including a reduced intake of dietary calories without malnutrition, or a restriction of specific dietary component may promote health benefits and decrease the incidence of aging-related comorbidities, thus representing intriguing potential approaches to improve healthy aging. However, the relationship between nutrition, health and aging is still not fully understood as well as the mechanisms by which nutrients and nutritional status may affect health span and longevity in model organisms. The broad effect of different nutritional conditions on health span and longevity occurs through multiple mechanisms that involve evolutionary conserved nutrient-sensing pathways in tissues and organs. These pathways interacting each other include the evolutionary conserved key regulators mammalian target of rapamycin, AMP-activated protein kinase, insulin/insulin-like growth factor 1 pathway and sirtuins.

1. Introduction

In humans the life span is dependent on genetic, environmental and lifestyle factors. The genetic components contribute for about 20–25%, while some components of lifestyle seem to play major roles [1][2]. Recent advances in the field of gerontology are showing that aging should be viewed as adaptive and amenable to interventions aimed at extending health span and life span. Over the last several decades, improvements of several lifestyle components such as nutrition, and hygiene education, together with medical advances and therapy have led to a significant increase in life expectancy. However, longer life expectancy can also lead to an increase of the number of people suffering from age-related diseases and age represents the main risk factor for all major life-threatening disorders. The fact that health span is not growing in the same way as life span is a source of great concern and it has raised interest among the scientific and medical community to study and elaborate strategies to improve health span. We highlight the importance of human studies to better understand interventions that could counteract the functional decline of tissues and organs and prevent the accumulation of molecular damage leading to multiple chronic diseases. Interestingly, the most effective interventions to improve healthy senescence to date converge on only a few cellular and biochemical processes, in particular nutrient signaling, mitochondrial efficiency, proteostasis, autophagy, microbiota modulation. The role of the genotype in aging and longevity is an important issue that we do not have the ability to favorably modify. However, growing evidence has shown that epigenetic changes could interfere with the genetic profile to deeply affect health span and, in some situations, to be even more important than the genetic profile. Indeed, alterations in DNA methylation, post-translational modification of histones and changes in the organization of chromatin have been demonstrated to influence health span and life span in several animal models (invertebrate organisms and vertebrate models, mostly rodents) [3].

Epidemiological, clinical and experimental studies actually showed that what we eat and how much we consume contributes to determine our health span [1]. Recently Longo hypothesized the existence of multiple “longevity programs” which are selected according to the availability of nutrients and that the key event for increased health span is the activation of regenerative processes that lead to “rejuvenation” also independently of aging rate [4]. The anabolic processes such as growth, reproduction and nutrient

storage are promoted by the excess of nutrients, whereas nutrient limitation stimulates catabolism in order to serve energy and essential functions. Such pathways, which interact with each other, include the evolutionarily conserved key regulators mammalian target of rapamycin (mTOR), insulin and insulin-like growth factor 1 (IGF1) pathways, AMP-activated protein kinase (AMPK), sirtuins (SIRTs) and fibroblast growth factor 21 (FGF21) pathways. Their interrelations are presently under continuous and widespread investigation, and the complex network by which the nutrient signaling pathways mediate the effects of nutrients or various feeding regimens remains to be fully understood.

2. Nutrient Sensors that Potentially Affect Health Span

2.1. Sirtuin 1 (SIRT1)

SIRTs are crucial nutrient sensors extensively studied in the last decade because of their pleiotropic functions potentially affecting health span. In mammals, the SIRT family includes seven members (SIRT1-7) differentially located in cell compartments and exerting various roles. SIRTs affect the activity of proteins implicated in metabolism, oxidative stress, cell survival, autophagy, with important consequences on aging. Among SIRTs, SIRT1 is the best described in literature. This enzyme, like other components of the family, is a deacetylase and depends on NAD^+ for its activity. Since this molecule accumulates in the cell typically during fasting or exercise, SIRT1 results to be activated in these situations of low energy levels [5]. Decreased NAD^+ levels with aging in part explains the decrease of SIRT1 activity in elderly people. Therefore, this enzyme has been included among the most promising nutritional biomarkers [6]. SIRT1 deacetylase activity influences the function of many proteins implicated in cell metabolism. In this regard it has been shown that almost all enzymes of anabolic and catabolic pathways are highly acetylated [7]. Thus, SIRT1 activity may impact gluconeogenesis, glycolysis, fatty acid oxidation, tricarboxylic acid (TCA) cycle and oxidative phosphorylation. SIRT1 also deacetylates many transcription factors that control the alternative for the cell between an oxidative and an anabolic strategy. In liver SIRT1 deacetylates the transcription factor sterol regulatory element-binding protein 1c (SREPB1c), thus reducing its affinity for promoters of the lipogenic targets genes [8]. In adipocytes, SIRT1 favors corepressor efficiency on peroxisome proliferator-activated receptor γ (PPARγ) reducing adipogenesis. These effects increase fat mobilization instead of storage and induce favorable cellular and health changes [9]. SIRT1 expression increases during energy starvation in both mice and humans and declines under high fat diet or obesity. Studies in mice have also shown that SIRT1 overexpression conveys similar beneficial health effects as low calorie diets and protects various markers of health upon diet-, injury- and disease-related stressors [10][11].

SIRT1 has been extensively implicated in the prolongevity effect of caloric restriction (CR) in model organisms. Moreover, this enzyme represents a target in the mechanism of action of bioactive and health-promoting compounds, such as resveratrol and other polyphenols, also called CR mimetics (CRMs) [12] SIRTs have been extensively implicated in several age-related degenerative diseases, such as cancer, diabetes, cardiovascular disease and neurodegenerative disorders. These enzymes may exert neuroprotective effects and counteract some kinds of tumors, also by stimulating autophagy, a process of cellular “self-digestion”, an efficient way of biochemical recycling needed for maintaining cellular homeostasis and influence health span [13][14]. Both SIRT1 and SIRT3 activate autophagic machinery by deacetylation of key autophagic components [14]. Activation of autophagy can consequently activate mitophagy, leading to selective clearance of damaged mitochondria. In mitochondria, SIRT3 also deacetylates forkhead box O transcription factors (FOXOs) and mitochondrial superoxide dismutase (SOD2), resulting in greater respiratory efficiency, apoptotic resistance and protection from reactive oxygen species [15][16][17][18].

Stimulation of autophagy by SIRTs may be particularly relevant in elderly people as during aging a reduction in proteolytic activity and autophagic function has been reported, with a consequent accumulation of damaged proteins [19]. Reduced SIRT activity in aging has been in part related to decreased availability of NAD^+ for deacetylase reactions due to higher activation of poly-[ADP-ribose]

polymerase 1 (PARP1) in elderly people. This enzyme catalyzes ADP-ribosylation reactions and also needs NAD^+ as a cosubstrate. PARP1 plays a crucial role in mechanisms of DNA repair. It has been demonstrated that the inhibition of PARP1 affects SIRT1 activity and oxidative metabolism by raising NAD^+ levels [20]. Recently the relation between SIRT1 and autophagy has been further studied and a more complicated picture has been revealed. Indeed, new evidence reported that autophagy may downregulate SIRT1 contributing to its loss in senescence and ageing in several tissues related to the immune and hematopoietic system [21].

2.2. AMP-Activated Protein Kinase (AMPK)

AMPK is a conserved, energy-sensing serine/threonine kinase which is activated in case of low cellular energy levels resulting in increased levels of AMP. Indeed, the catalytic subunit of this enzyme (α) is controlled by the regulatory subunits β and γ, responding to the direct interaction with AMP and ADP and to the upstream kinases liver kinase B1 (LKB1) or calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) [22].

AMPK stimulates catabolic processes that produce energy. Indeed, this enzyme is able to activate the uptake and the utilization of glucose and fatty acids, mitochondrial biogenesis and autophagy. At the same time the activation of AMPK inhibits by phosphorylation acetyl-CoA carboxylases (ACCs), glycerol phosphate acyl-transferases (GPATs), 3-hydroxyl-3-methylglutaryl CoA reductase (HMGCR) and glycogen synthase, thus repressing anabolic processes like fatty acid, triglyceride, cholesterol and glycogen biosynthesis [23][24]. Several transcription factors, like carbohydrate-responsive element-binding protein (ChREBP) and SREBP1c, are inhibited in liver by AMPK, which contributes to reprogram cell metabolism [25]. AMPK also inhibits a pro-inflammatory transcription factor, nuclear factor kB (NF-kB), by phosphorylating FOXO [26]. Conversely, AMPK increases the activity of the deacetylase SIRT1 and of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) [24]. AMPK has been considered a “pro-longevity kinase”, since its activation would be sufficient to extend lifespan in model organisms [27].

Activation of AMPK results in improvement of insulin sensitivity, fatty acid metabolism, mitochondrial performance and, in model organisms, this enhanced longevity [27][28]. AMPK appears to be beneficial for health, in particular in the context of obesity, nonalcoholic fatty acid disease (NAFLD), atherosclerosis and diabetes; therefore, therapeutic strategies aimed at activating AMPK remain promising for the treatment of metabolic diseases [28]. Activators of AMPK are many natural compounds, generally known as nutraceuticals, such as resveratrol, genistein, gallic acid, betaine. Additionally, some known small molecules are direct AMPK agonists, such as aspirin, rapamycin and metformin [27]. Of special relevance is that the antidiabetic drug metformin is a potent inducer of AMPK and has been suggested to be also a geroprotective agent. Metformin has been reported to reduce the risk of several aging-associated pathological conditions, including cardio-metabolic and neurodegenerative disorders, frailty and cancer in humans [29].

2.3. Forkhead Box O transcription Factors (FOXOs)

FOXO family transcription factors are central regulators of metabolic homeostasis, redox balance and stress response. In humans, the FOXO family comprises FOXO1, FOXO3, FOXO4 and FOXO6. Most FOXO genes are known to be implicated in human longevity [30]. In particular, the association of FOXO3 with human longevity has been evidenced by many research groups on different long-lived subjects [31][32].

FOXO functions are critical for coordinating a response to environmental fluctuations in order to maintain cellular homeostasis and support healthy aging [32]. FOXOs respond to a wide range of stimuli, including growth factors, hormones, oxidative and genotoxic stress and low nutrient availability. Downstream functions of FOXOs are conserved across species and include regulation of a variety of cellular processes and several longevity routes, such as autophagy, nutrient signaling, stress resistance, cell cycle arrest, suppression of inflammation and antioxidant activity (for a review: [33]). In the liver, low nutrient status

and thus low levels of insulin signaling activate FOXOs to restore glucose levels via glycogenolysis and gluconeogenesis. Then, FOXO delivers a metabolic shift from glucose to fatty acid oxidation and enhances mitochondrial biogenesis. In human skeletal muscle the activation of FOXO3 by CR promotes upregulation of several anti-aging genes, including those responsible for antioxidant enzymes, DNA repair and autophagy [34].

FOXO activity is tightly regulated at the post-translational level in all species. FOXOs receive inputs from various signaling pathways in the form of covalent modifications, including phosphorylation, acetylation, methylation and ubiquitination, as well as of protein–protein interactions. FOXO3 in particular is activated through phosphorylation and deacetylation. Insulin signals through phosphoinositide 3-kinase (PI3K)-AKT phosphorylates FOXO proteins thus triggering their inactivation and nuclear exclusion. Phosphatase and tensin homolog (PTEN) inhibit the activation of PI3K thus promoting FOXO activation and nuclear localization. AMPK directly phosphorylates FOXO3 at six serine/threonine residues that are distinct from the AKT phosphosites and this event promotes interaction between cofactors and FOXO3 to affect specific target genes. Fasting conditions can up-regulate SIRT1, which deacetylases and activates FOXOs in the liver. This cellular context involves dual regulation: low insulin levels drive FOXOs into the nucleus, which are then further activated through deacetylation by SIRT1.

Although most studies have focused on post-translational regulation of FOXO factors, several groups have reported post-transcriptional regulation by microRNAs (miRNAs) [35]. Indeed, many miRNAs have been found to directly modulate FOXO transcript stability or translation. Moreover, this post-transcriptional regulation can also occur by RNA-binding proteins. These proteins act as mRNA-stabilizing, or regulators of mRNA splicing, transport and translation. Thus, the resulting picture of the post-transcriptional regulation of FOXO activity is quite complex and seems to respond to stress stimuli to promote adaptation in a variety of cell types and tissues and under diverse physiological and pathological conditions, including oxidative stress, cancer and age-related diseases.

2.4. Fibroblast Growth Factor 21 (FGF21)

FGF21 is an important mediator with a critical role in the transition from fasting to refeeding status. This molecule is mainly synthesized by the liver, which, during fasting, secretes it to coordinate the metabolic response. FGF21 activates fatty acid oxidation and ketogenesis in liver and, specifically in humans, this hepatokine is involved in the late adaptive response to fasting (7–10 days). In this condition, FGF21 induces the expression of PGC1α and late hepatic gluconeogenesis, but not glycogenolysis in order to spare hepatic residual glycogen reserves. Moreover, in this situation of low energy, FGF21 induces lipolysis and the production of adiponectin in adipose tissue and promotes AMPK-SIRT-PGC1α network. Conversely, FGF21 has an inhibitory effect on insulin/IGF1 signaling (IIS) pathway [36].

Interestingly, FGF21 seems to mimic CR, having a similar effect on gene expression in liver. Thus, it is conceivable that it has a potential role as a factor promoting life span, such as CR [37]. Some data suggested that the production of FGF21 is dependent on protein restriction, and in particular dependent on the low level of methionine intake [38][39]. Moreover, low protein-rich carbohydrate diets seem to be more effective in the stimulation of FGF21 production [40].

Adipose tissue is an additional production site of FGF21, however in this case it acts just locally, and its role is in close connection with the refeeding. Indeed, when there is the transition from late fasting (during which FGF21 by the liver operates) to refeeding (when liver stops to synthetize it), adipose tissue produces FGF21 in order to promote insulin-stimulated glucose uptake and counteract insulin insensitivity induced by the released fatty acids during fasting [41]. FGF21 also plays a role in the activation of brown adipose cells and in the “browning” mechanism of white adipocytes. In light of this, FGF21 receptor agonists are emerging as therapeutic drugs for the treatment of obesity-related diseases [42][43].

Recently, FGF21 as well as the fibroblast growth factor 19 have been involved in the signaling pathway that control muscle mass [44]. In normal conditions basal expression of FGF21 in muscle is low, however

different physiological and pathological conditions such as exercise, fasting condition or mitochondrial stress may increase its level [45]. FGF21 has been reported to control muscle mass through the regulation of anabolic/catabolic balance and mitophagy [46]. Moreover, circulating FGF21 levels positively correlate with aging [47] and age-related sarcopenia [48]. This increase may also be a compensatory response to mitochondrial dysfunction to counteract energy insufficiency [49][50]. However, the direct contribution of this factor to muscle dysfunction related to aging has not been investigated yet.

2.5. Insulin-Like Growth Factor 1 (IGF1) and Growth Hormone (GH)

Components of IIS pathway are hormones, such as growth hormone (GH), insulin and IGF1, their specific receptors, proteins and kinases downstream able to transduce the signal, as well as plasmatic IGF1 binding proteins. IGF1 is an anabolic hormone mainly produced in the liver and also locally expressed in peripheral tissues. IGF1 is under the control of GH from the pituitary and the secretion of GH/IGF1 is essential for normal growth in children and for the maintenance of anabolic processes in adults. The activity of IGF1 is influenced by six binding proteins (IGFBPs), which also have independent biological actions [51].

Although IGF1 pathways are essential, various studies in model organisms support the hypothesis that a reduction of this signaling can exert life span-extending effects [52][53][54][55]. Considering that the levels of GH and IGF1 are down-modulated during normal or accelerated aging, whereas constitutively low IIS promotes longevity, it has been hypothesized that IIS decrease is a response to some damage naturally occurring during metabolism and cell growth. Thus, organisms with a constitutively decreased IIS have longer life span as their metabolism and damage rates are lower, while during aging the organism try to survive by decreasing IIS [56].

Low IGF1 levels in humans can predict survival in people with exceptional longevity [57] and one mechanism might be related to a lower risk of developing cancers [58]. Laron's syndrome (LS) is a rare genetic disorder presenting a dissociation between GH and IGF1 activity. The number of known and/or published LS patients is around 350. Most cases have been reported from the Mediterranean region and Southern Ecuador, and a few cases from South America, as recently reviewed [59][60][61]. LS is characterized by insensitivity to GH. Up to the present time, over 70 mutations of GH receptor (GHR) genes have been identified leading to GH/IGF1 signaling pathway defect. The biochemical features typical of LS patients are high serum level of GH and low free IGF1 concentrations. People affected by LS are characterized by dwarfism and obesity and have a tendency to develop hyperlipidemia, but surprisingly have a very low risk to manifest aging-related pathologies such as diabetes and cancer [62][63]. Additionally, other studies in humans showed a positive association between low IGF1 activity and longevity [64].

However, not all studies found a correlation between low IGF1 and longevity in humans [64]. For example, in a cohort of 252 centenarians, low IGF1 and IGFBP3 serum concentrations were associated with increased mortality [65]. Another study also showed that healthy centenarians had a plasma IGF1/IGFBP3 molar ratio greater than aged subjects [66] . Moreover, in the elderly the GH/IGF1 system might elicit a protective and beneficial effect which is mainly related to its anabolic activity, especially on muscle and bone [67].

2.6. Mammalian Target of Rapamycin (mTOR)

The "mammalian target of rapamycin" (mTOR), is a serine/threonine protein kinase which is involved in regulating protein synthesis, cellular growth and proliferation. This enzyme receives and integrates many hormonal stimuli coming from the IIS pathway as well as signals coming from specific nutrients, in particular amino acids (AAs) like leucine [68]. mTOR can participate to two different complexes with many other proteins: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is implicated in most of actions exerted by this kinase. In particular, by the activation of this complex, mTOR transduces anabolic signals. Its main functions are regulation of the biogenesis of ribosomes and the synthesis of

proteins and nucleotides according to cell needs. Moreover, mTOR stimulates lipogenesis, glycolysis and pentose phosphate pathway. mTOR downregulates catabolic pathways and suppresses protein turnover mainly via the inhibition of autophagy. The downregulation of mTOR activity suppresses protein synthesis and this event allows endogenous protein repair and degradation machinery to preserve the correct proteostasis and attenuating possible aggregate-related damages. The activity of mTOR is repressed in fasting or stress conditions, when decreased substrate availability counteracts anabolic pathways.

Several studies in key model organisms showed that the mTOR pathway is related to life span and health span and reduced mTOR signaling through genetic or pharmacological interventions results in life span extension in yeast, worms, flies and mice [69][70][71]. mTOR activation may exert a crucial role in aging process. Many age-associated pathologies, which are characterized by hyper-functionality of proliferative processes, may be prevented by a general decrease in protein synthesis. However, in elderly people mTOR may show the beneficial outcomes of its activity, preventing sarcopenia and lean mass loss. In conclusion, there is a general consensus that this kinase can promote metabolic health or disease depending on human age and on particular signaling of specific tissues [72].

Compared with mTORC1, much less is known about mTORC2 upstream regulation and downstream outputs, and the relationship between the two complexes is still unclear. Although the implication of mTORC2 in human health span and life span has been less studied, it is known that in mammalian cells, mTORC2 interacts with IIS-mTOR pathway activating AKT to repress FOXO1 and FOXO3, which affect longevity [73]. Moreover, the selective suppression of mTORC2 seems to reduce life span and to be associated with changes in hormone sensitivity and metabolism (for example, insulin resistance), with a negative impact on health span [74]. Thus, a possible strategy to counteract age-related pathologies and improve longevity and health span could be the use of specific inhibitors to suppress mTORC1 with minor effects on mTORC2.

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Keywords

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