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Review

Dietary restriction, mitochondrial function and aging: from yeast to humans ☆

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ABSTRACT

Dietary restriction (DR) attenuates many detrimental effects of aging and consequently promotes health and increases longevity across organisms. While over the last 15 years extensive research has been devoted towards understanding the biology of aging, the precise mechanistic aspects of DR are yet to be settled. Abundant experimental evidence indicates that the DR effect on stimulating health impinges several metabolic and stress-resistance pathways. Downstream effects of these pathways include a reduction in cellular damage induced by oxidative stress, enhanced efficiency of mitochondrial functions and maintenance of mitochondrial dynamics and quality control, thereby attenuating age-related declines in mitochondrial function. However, the literature also accumulates conflicting evidence regarding how DR ameliorates mitochondrial performance and whether that is enough to slow age-dependent cellular and organismal deterioration. Here, we will summarize the current knowledge about how and to which extent the influence of different DR regimes on mitochondrial biogenesis and function contribute to postpone the detrimental effects of aging on healthspan and lifespan. This article is part of a Special Issue entitled: Mitochondrial Dysfunction in Aging.

1. Introduction

Altered mitochondrial metabolism is a hallmark of aging [1]. Reduced respiratory capacity and increased oxidative stress associated with age have been reported in an array of tissues, including muscle and several brain regions [1]. The mitochondrial/free radical theory of aging explains many aspects of cell and organismal aging. This theory proposes that mitochondrial energy production decline and mitochondrial reactive oxygen species (ROS)-induced damage are the major causes of aging [2]. Although this is a longstanding theory, evidence supporting and contradicting its postulates, gathered from studies on diverse model organisms, accumulate in the literature [3–6]. Overall, these studies suggest that although oxidative damage is an important contributor, there is more to aging than damage mediated by ROS. On the other hand, preservation of mitochondrial functions and enhancement of mitochondrial biogenesis are critical components of several mechanisms promoting health and lifespan extension that are conserved from yeast to mammals [7–9].

Research efforts have been devoted to strategies for longevity extension, regarded as a retardation of biological aging. Although longevity extension strategies will not eliminate aging-related diseases, they are expected to postpone their age of onset, thus contributing to the objective of extending healthspan [10]. Calorie restriction (CR), which usually refers to a 20–40% reduction in calorie intake without malnutrition, is the most robust environmental intervention that slows aging and extends lifespan in yeast, worms, fruit flies, rodents, and perhaps also in primates [10–13], through largely conserved mechanisms.

Studies to understand the molecular mechanisms of CR-mediated longevity in simple research models, such as the yeast *Saccharomyces cerevisiae*, have allowed for the identification of several longevity genes and pathways. In yeast, CR down-regulates the conserved signaling pathways Ras/cAMP/PKA, TOR (target of rapamycin), and its major target the serine/threonine protein kinase Sch9, all of which integrate nutrient and other environmental cues to regulate cell growth, division, and lifespan [12]. Deletion of *RAS2*, *TOR1* or *SCH9* enhances cellular protection against thermal and oxidative stresses and extends yeast chronological lifespan (CLS) [14]. Inhibition of these pathways converges on the activation of stress resistance transcription factors that

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positively regulate the expression of cell protection systems; e.g. chaperones to combat protein misfolding, free radical scavengers such as catalase and mitochondrial superoxide dismutase (SOD2), and accumulation of store nutrients (trehalose and glycogen in yeast cells). The key components of these pathways also regulate stress resistance and lifespan in higher eukaryotes [15]. For example, both serine/threonine-specific protein kinases Akt and S6K (ribosomal protein S6 kinase), homologues of yeast *SCH9*, regulate lifespan in higher eukaryotes and inhibition of TOR/S6K signaling extends lifespan in worms, flies, and mice [16,17]. Also, mice deficient in elements of the RAS pathway have extended health- and lifespan [18]. Together, these studies have highlighted an important role of nutrient-sensing pathways in lifespan modulation and CR-induced lifespan extension, suggesting a common evolutionary origin of aging regulation [14].

The longevity pathways play an important role in the regulation of mitochondrial biogenesis and/or function in yeast and higher eukaryotes including mammals [19,20]. For example, deletion of the *TOR1* gene extends yeast CLS in part by increasing mitochondrial mass and respiration [19] and by promoting adaptive mitochondrial ROS signaling [21]. The Ras/cAMP/PKA pathway senses excessive ROS to signal to the Hap2,3,4,5 transcriptional system and down-regulates mitochondrial biogenesis [22]. Also, in mammals, modulation of mitochondrial biogenesis and metabolism through the TOR, Akt1, and Ras pathways involves the peroxisome proliferator activated receptor gamma transcriptional coactivator-1α (PGC-1α) [20]. PGC-1α is a master regulator of mitochondrial biogenesis that coactivates the nuclear respiratory factors (NRF-1 and NRF-2), which induce the transcription of genes involved in mitochondrial biogenesis.

Numerous recent studies on model organisms and even in humans suggest that the health-promoting effect of CR interventions can be achieved by decreases in specific dietary components. Interventions such as protein restriction (PR), methionine restriction, and alternate day fasting while maintaining overall calorie intake, have outcomes similar to that observed following a CR diet. It is also becoming evident that the balance of nutrients such as carbohydrates, proteins, amino acids, fats, and minerals may play an essential role in regulating both lifespan and healthspan. Dietary restriction (DR) studies in yeast, fruit flies, rodents, and primates are beginning to clarify the dietary factor/s that cause/s the beneficial changes and the role of mitochondrial function in the mechanism/s involved.

The effects of DR on aging and healthspan have been covered by many recent reviews, focusing on simple model organisms or mammals [15,23,24], mostly on calorie restriction (CR) and less frequently on protein and amino acid restriction [15,25]. In this manuscript, we will cover the information gained from exploiting yeast models of aging and will subsequently focus on studies performed in higher organisms to summarize the current knowledge about the influence of different DR regimes on mitochondrial biogenesis and function, the pathways involved, and the extent to which maintaining mitochondrial health through DR contributes to postpone the detrimental effects of aging on health- and lifespan.

2. Dietary Restriction, Mitochondria, Aging and Longevity in the Yeast *Saccharomyces Cerevisiae*

2.1. Mitochondrial determinants of yeast longevity

The facultative aerobe/anaerobe metabolism of the yeast *Saccharomyces cerevisiae* makes this organism a good model for mitochondrial studies. Over the last three decades, *S. cerevisiae* models of aging have contributed to the discovery of conserved longevity factors that modulate aging in mammals [26,27]. Two models of aging, the replicative lifespan (RLS) model and the chronological lifespan (CLS) model, have been established in this organism. RLS is defined as the number of asymmetric mitotic divisions a mother cell can undergo prior to cell cycle arrest. This yeast mother-cell-specific aging constitutes a model of replicative aging as it occurs in fibroblasts, lymphocytes, or stem cell populations of higher eukaryotes [26–28]. CLS, defined as the capacity of postdiauxic, stationary (G_0) cultures to maintain viability over time, is, on the other hand, a model for the aging process of postmitotic cells such as mature neurons and muscle cells [27,29].

In yeast, mitochondrial function is important for both replicative and chronological lifespan, as mitochondrial oxidative phosphorylation (OXPHOS) function deteriorates and mitochondrial ROS generation amplifies with increasing age [29,30]. During replicative aging, the changes the mother cell undergoes include an increased generation time, increased size, declined mating ability, nucleolar and mitochondrial fragmentation, and the accumulation of both extra-chromosomal rDNA circles (ERCs) and oxidatively damaged proteins [31,32]. The effect of mitochondrial dysfunction on RLS may be not fully dependent of the OXPHOS capacity of the organelle, since the literature accumulates examples of mutations limiting respiration that either curtail or prolong RLS [30]. However, RLS is extended by enhancement of mitochondrial biogenesis [33], and mitochondrial function links RLS and CLS [34]. Additional parameters, such as proper mitochondrial segregation and inheritance [33], prevention of mitochondrial proteotoxic stress [35,36], and maintenance of proper nuclear-mitochondrial communication through activation of mitochondrial retrograde signaling pathways [37] are important regulators of RLS. For example, a mechanism exists for retaining "less fit" mitochondria within the mother cell, thus preventing their transmission into the daughter cell [38]. Thanks to asymmetrical protein inheritance, daughter cells are able to eliminate ROS after completion of cytokinesis [39], ensuring that the new cell is born with a full replicative potential. Additionally, special mention also go to mitochondrial retrograde responses that have emerged as important players in aging and longevity [40], further emphasizing the importance of metabolic control in determining these processes. In yeast, the first described mitochondria-to-nucleus retrograde (RTG) pathway senses decline in mitochondrial membrane potential and initiates a transcriptional response to compensate for mitochondrial dysfunction by reconfiguring metabolism [37,41,42]. The RTG response increases the expression of genes involved in anaplerotic pathways that supply acetyl-CoA and citrate to mitochondria, including genes involved in peroxisomal biogenesis and fatty acid β-oxidation [37]. The TCA cycle is disrupted in respiratory-deficient yeast, and peroxisomal anaplerotic contributions become critical to maintenance of an adequate pool of α-ketoglutarate, essential for cellular redox maintenance and the generation of glutamate, a basic source of nitrogen [37]. Three proteins, Rtg1, Rtg2, and Rtg3, are required for the retrograde response in yeast [43,44]. Rtg2 transduces the mitochondrial dysfunction signal, specifically the loss of mitochondrial membrane potential [42], and promotes the formation of the active heterodimeric Rtg1-Rtg3 transcription factor that translocates to the nucleus and binds to the retrograde response element in the promoters of retrograde response genes [37,43,44]. Activation of the RTG pathway has been shown to extend RLS in certain conditions [42]. Other organelles also influence mitochondrial fitness and overall replicative aging [45]. Vacuolar acidification decreases with replicative age and this parameter correlates with loss of mitochondrial membrane potential [45]. Thus, multiple factors influence mitochondrial quality control, ultimately affecting RLS.

Chronologically aging cells require mitochondrial respiration along their lifespan [46]. For CLS studies, yeast cells are usually aged in media containing 2% glucose. Under these conditions, cells divide exponentially producing energy preferentially by fermentation while respiration is repressed in a glucose-concentration-dependent manner. As glucose is being consumed, growth slows down and the diauxic shift occurs, which involves a shift from fermentation to respiration, the activation of stress resistance mechanisms, and the accumulation of nutrient stores (glycogen and trehalose) to be used later in the stationary phase in which the metabolic rate is significantly reduced. Mitochondrial respiration during exponential growth is essential for strains to achieve a standard wild-type CLS [47–49]. However, we have shown

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