



Mitochondrial function and nutrient sensing pathways in ageing: enhancing longevity through dietary interventions

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Abstract Ageing is accompanied by alterations in several biochemical processes, highly influenced by its environment. It is controlled by the interactions at various levels of biological hierarchy. To maintain homeostasis, a number of nutrient sensors respond to the nutritional status of the cell and control its energy metabolism. Mitochondrial physiology is influenced by the energy status of the cell. The alterations in mitochondrial physiology and the network of nutrient sensors result in mitochondrial damage leading to age related metabolic degeneration and diseases. Calorie restriction (CR) has proved to be as the most successful intervention to achieve the goal of longevity and healthspan. CR elicits a hormetic response and regulates metabolism by modulating these networks. In this review, the authors summarize the interdependent relationship between mitochondrial physiology and nutrient sensors during the ageing process and their role in regulating metabolism.

Keywords Mitochondria · AMPK · Sirtuins · mTOR · Ageing · Dietary restriction

Introduction

Ageing, a time-dependent phenomenon, is accompanied with a decline in homeostatic balance and it is mostly inevitable by living organisms. It is a multi-faceted, heterogeneous, progressive process, interacting at different levels of biological hierarchy – molecular, cellular and tissue level, causing various organs to age differently (Jones et al. 2014). A number of age-associated processes have been analyzed, as potential drivers of ageing, as they interact with each other to maintain homeostasis at different levels of organization (Kennedy et al. 2014). Interactions between genetic and epigenetic factors control ageing and modulating these factors extend lifespan. Ageing poses as the primary risk factor to various chronic diseases like type 2 diabetes mellitus (T2DM), Alzheimer’s disease (AD), Parkinson’s disease (PD), cardiovascular disease, cancers, sarcopenia and immune system disorders; and as the most significant cause of human morbidity and mortality (Aunan et al. 2017). Various theories have been proposed in an attempt to explain the phenomenon of ageing (López-Otín et al. 2013; Sharma and Dkhar 2014; Lipsky and Kin 2015).

Ageing in itself is an inclusive term for a number of biological processes with multiple aspects, which have been described by López-Otín et al. (2013) as hallmarks of ageing. Among the hallmarks, the dysregulation of mitochondrial function and a gradual decline in functioning of nutrient sensing pathways

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act as antagonistic hallmarks of ageing. These hallmarks are interconnected as they encroach upon cellular metabolism. They respond to changes in the environment—nutrient excess or scarcity, physical or chemical stress and exposure to microorganisms. Age-related deterioration of one of the above-mentioned processes has a profound effect on the other. The deregulation of these pathways drives the cell towards a senescent state, which contributes to ageing phenotype and, eventually, drives the organism susceptible to chronic age-related diseases. Thus, targeting metabolic regulation could be an encouraging approach towards extending human healthspan and lifespan.

Dietary interventions, such as calorie restriction, intermittent fasting, usage of CR mimetics, have shown to be of great importance in altering mitochondrial dysregulation and nutrient sensing pathways in ageing organisms, thereby extending their healthspan part of lifespan. This review focuses on two of the hallmarks of ageing, viz., mitochondrial dysfunction and declining function of the nutrient sensing pathways, how nutrient sensors regulate mitochondrial function and how dietary factors alleviate the ill effects of ageing associated with these two hallmarks.

Mitochondrial association during ageing

Mitochondria, as the powerhouse of the cells, provide the energy requirement for aerobic organisms to perform all the activities in the form of adenosine triphosphate (ATP) through the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC), and are the major sources of intracellular reactive oxygen species (ROS). They are also crucial for basic cellular functions, such as redox balance, signalling transduction, metabolic homeostasis, cell differentiation and senescence. Thus, their dysfunction leads to reduction in the ATP production, elevated production of ROS, reduced antioxidant resistance and metabolic disorders, including various age-related neurological, fibrotic and cardiovascular diseases (Boengler et al. 2017; López-Lluch et al. 2018; Zhu et al. 2019; Li et al. 2020). ROS, under normal physiological conditions, have various important functions in regulating cellular metabolism. Hydrogen peroxide (H_2O_2) and superoxide ($\text{O}_2^{\cdot-}$) are two important ROS which act as

signalling molecules in regulating cell growth, differentiation and death, activate mitogenic-activated protein and also take part in an organism's immune response against a number of infections. H_2O_2 helps in regulating the expression of a number of genes, including nuclear factor erythroid-2-related factor 2 (Nrf2), activator protein (AP-1), cAMP response element binding protein (CREB), nuclear factor kappa B (NF- κ B), heat shock factor 1 (HSF1), hypoxia inducible factor 1 (HIF-1), tumour protein p53 (TP53), neurogenic locus notch homolog protein (NOTCH), and specificity protein 1 (SP1) (Marinho et al. 2014; Sies 2017). Proteins with sulfhydryl groups can be directly affected by ROS through the oxidation of their thiol moiety. They can also increase the capillary walls' permeability, thereby stimulating glucose transport into the cells as well as that of serotonin into platelets (Droge 2002; Giorgi et al. 2018). However, uninhibited production of ROS may incite oxidative damages to the major cellular components (proteins, lipids, nucleic acids) due to their high reactivity and are, therefore, likely to be toxic, mutagenic, or carcinogenic. Free radical reaction intermediate products, e.g., peroxynitrite and lipid hydroperoxides, can alter various components of the cell (Giorgi et al. 2018).

In 1954, the free radical theory of ageing (FRTA) was proposed by Denham Harman, linking oxidative stress and ageing (Harman 1956). It was later developed as the mitochondrial free radical theory of ageing (MFRTA), stating that mitochondrial dysfunction and subjection to subsequently heightened ROS production give rise to a vicious loop causing damages to cell and its components, consequently leading to death (Harman 1972). Though the theory initially received not so much enthusiasm, ROS have shown to be of great importance during the process of ageing. Studies have shown the association of oxidative damages to deoxyribonucleic acid (DNA), proteins and lipids with uncontrolled production of ROS, impaired mitochondrial function and untimely cell death or senescence (Sohal and Weindruch 1996; Bokov et al. 2004). Increased production of ROS has also been linked to mitochondrial oxidative damage, accompanied by a decrease in the copy number of mitochondria (Herbener 1976; Yen et al. 1989; Lambert et al. 2007; Cocheme et al. 2011). These changes have shown to be associated with characteristic features of human ageing, such as loss of hair, reduced fat and

weight, decrease in the bone density and cardiomyopathy (Trifunovic et al. 2004).

Mitochondrial ROS regulation during ageing

Throughout the life of a cell, there is a constant mitochondrial ROS generation, resulting in an age-associated chronic oxidative stress, accounting for mitochondria being crucial players during ageing (Miquel et al. 1980; Santos et al. 2013). Complexes of the ETC can get assembled into functionally and structurally larger units, also known as ‘respirasomes’, that allow minimizing the diffusion distances of substrates for a more effective electron flow through the ETC. These supercomplexes have been proposed to be linked to an age-dependent destabilization, contributing to the development of an ageing phenotype of the mitochondria, especially in post-mitotic tissues (Gomez and Hagen 2012). The rate at which these ETC complexes are assembled affects the ROS production capacity of the mitochondria (Genova et al., 2015; Moreno-Loshuertos et al. 2016), suggesting that the inability to form large units or their continual degradation might be an important factor in bringing about age-associated heightened ROS production and oxidative stress (Genova et al. 2015). Mitochondrial DNA (mtDNA), mitochondrial enzymes and lipids are the primary targets of ROS. Another factor favouring the adverse consequences of oxidative stress resulting in the accumulation of damaged mtDNA is the close vicinity of the DNA from the sites for ROS production in the ETC (Yen et al. 1989; Lambert et al. 2007; Cocheme et al. 2011). On contrary to their destructive property, ROS, when present lower than a level that can be toxic, are essential for normal physiological functions and involved in many signal transductions, such as regulation of autophagy and inflammatory responses (Whitehall et al. 2020).

During ageing, along with the increase in the ROS production, there is an associated decline in the antioxidative defense capacity, thereby increasing the deteriorating effects of oxidative stress. This successively leads to the reversible oxidation of the thiol groups, disrupting the antioxidative enzyme activity that can lead to harmful changes in the structure and function of various biomolecules (Freitas et al. 2016). In *Drosophila melanogaster*, it was observed that overexpression of antioxidative enzymes, such as superoxide dismutase (SOD) and catalase, protects

the DNA from the harmful effects of ROS by decreasing their production, ultimately extending the organism’s lifespan (Orr and Sohal 1994; Schriener et al. 2005). It was also observed that there is a higher level of such enzymes with decreased damage to the proteins and lipids, and adaptive mechanism of mitochondrial cysteine depletion in long-lived mice strains and other species (Pamplona et al. 2002; Rebrin and Sohal 2004; Moosmann and Behl 2008).

The negative correlation between ROS production and lifespan has been shown by various studies where hydrogen peroxide diffusing out from mitochondrial respiration was measured. Hydrogen peroxide production rate was much lower in the mitochondria of heart, brain and kidney of long-lived bats than that of short-lived shrew species (Brunet-Rossini 2004). Similar observation was also found in remarkably long-lived naked mole rat as compared to Fisher 344 rats (Csiszar et al. 2007). However, some studies have also shown the opposite results, depicting the positive correlation between ROS production and lifespan extension. In the vascular endothelial cells of long-lived Ames dwarf mice and their normal littermates, the production of hydrogen peroxide was more in the long-lived ones than that of the normal counterpart (Csiszar et al. 2008). In *Caenorhabditis elegans*, no effect on overall ROS was seen due to mutations in the mitochondria, even though the level of mitochondrial superoxide was elevated. In the mentioned study, unexpectedly, supplementing antioxidants shortened the lifespan of the mutants (Yang et al. 2010). Moreover, when antioxidative enzymes, like mitochondrial SOD2 (manganese superoxide dismutase, MnSOD) and glutathione peroxidase-1 (GPx-1), were silenced in mice, longevity of the organism was not affected despite the rise in level of oxidative stress (Perez et al. 2009; Zhang et al. 2009). Even so, evidence supporting the credibility of the MFRTA outweigh till date. Nonetheless, the contradictory observations made rather supports the theory known as mitohormesis, stating that the mitochondrial ROS in their moderate level have the capacity to activate mechanisms compensating protection of cellular organelles from the harmful effects of ROS and delay the appearance of phenotypes associated with ageing (Ristow and Zarse 2010). For example, in the case of *Drosophila* and young mice slight increase in the level of ROS have been associated with lifespan extension (Csiszar et al. 2008; Copeland et al. 2009; Basisty et al. 2016). The

finding that reducing elevated levels of mitochondrial ROS defends old mice from age-associated decline also suggests that decreasing ROS levels may help in delaying age-related diseases along with lifespan extension in ageing mammals (Schriner et al. 2005; Basisty et al. 2016). In human subjects, administering antioxidative compounds selegiline and vitamin E, singly or in combination, thereby downregulating the ROS concentration, have been seen to slow down the progression of AD (Sano et al. 1997). However, in PD, vitamin E failed to protect or delay the disease progression (Parkinson Study 1993) and was even found to be deleterious in some AD patients (Lloret et al. 2009).

Mitochondrial dysfunction in ageing

Mitochondrial dysfunction is one of the nine classical hallmarks of ageing (López-Otin et al. 2013). It is often linked with a number of processes such as decrease in the respiratory chain activity, fluxes in the TCA cycle, faulty regulation and function of mtDNA, elevated ROS level, intracellular calcium level changes and decline in the ATP level (de Almeida et al. 1989; Petrosillo et al. 2008; Emelyanova et al. 2018; Rottenberg and Hoek 2017; Li et al. 2020). Various studies have shown that mitochondrial quality control maintenance is of pivotal importance in fending off the process of ageing (Weber and Reichert 2010; Romanello et al. 2016). During ageing, there is an accumulation of damaged mitochondria with a mitochondrial turnover decline via mitophagy inhibition. Thus, striking a balance between generating new mitochondria and eliminating impaired ones is crucial for extending longevity (Chistiakov et al. 2014; Denzer et al. 2016). Impaired mitochondria release apoptogens into the cytoplasm due to the rupturing of the outer membrane leading to senescence during ageing (Daum et al. 2013). Mitochondrial dysfunction also adds to a number of metabolic disorders, cancer, neurodegeneration and various other pathologies (Thompson et al. 2015; Vincent et al. 2016; Spinelli et al. 2017; Reeve et al. 2018).

Mitochondria are interconnected dynamically, which enables them to share membranes, metabolites, proteins, solutes and electrochemical gradient as well (Tilokani et al. 2018). Mitochondrial dynamics is crucial in the regulation of mitochondrial function, quality control and senescence (Archer 2013).

It comprises of mitochondrial fission, fusion, movement and interconnection with other various cellular organelles, and is regulated by these afore mentioned processes through reconstructing the interconnected structure and function of mitochondria as a result of the nutrient level, signalling molecules and stress (Benard and Rossignol 2008; Sharma et al. 2019). Mitochondrial dynamics are deteriorated during ageing and in various age-associated diseases as seen with the presence of damaged mitochondrial physiology. Mitochondrial fission and fusion are the main modulators of mitochondrial dynamics. Mitochondrial fission is vital for removing aberrant mitochondria through mitophagy, mitochondrial transport and apoptosis via stress-induced hyperfission (Fannjiang et al. 2004; Malena et al. 2009; Thomenius et al. 2011; Mao et al. 2013). During ageing, some proteins associated with mitochondrial fission are found to be dysregulated, possibly leading to the altered mitochondrial dynamics in aged organisms. Cytosolic dynamin-related protein 1 (DRP1), the main protein coordinating mitochondrial fission, was found to be downregulated in aged mice skeletal muscle, and in human vascular endothelial cells (HUVECs) along with mitochondrial fission 1 protein (FIS1) (Mai et al. 2010; Leduc-Gaudet et al. 2015).

Inducing the expression of Drp1 midlife in *Drosophila* is seen to extend healthspan along with lifespan by enhancing mitochondrial respiration and autophagy. Moreover, mitochondrial fragmentation induction in the intestine of both *C. elegans* and flies is known for increasing lifespan (Han et al. 2017; Rana et al. 2017). These findings from different models used in ageing studies show that proteins associated mitochondrial fission decline with age and suggest regulating the expression of these proteins might have lifespan extension properties. In contradictory to the above observations, deletion of Drp1 ortholog Dmn1p delays ageing in yeast by inhibiting mitochondrial fission without hindering growth rate or fertility (Scheckhuber et al. 2007). Increasing mitochondrial fission in the skeletal muscle of mouse were also found to be associated with impairment of insulin signalling and mitochondrial dysfunction (Jheng et al. 2012). Therefore, increased or decreased mitochondrial function by elevating mitochondrial fission depends on the type of tissue or the organism (Sharma et al. 2019).

Membrane-bound dynamin related proteins help in attaining fusion of mitochondria. Fusion of mitochondrial outer membrane is mediated by mitofusin 1 (MFN1) and MFN2, and that of inner mitochondrial membrane by optic atrophy 1 (OPA1) (Hall et al. 2014) and loss of any of these proteins contribute to hyperfragmented mitochondrial network. Mitochondrial fusion helps in exchanging metabolites, membrane potential transmission, elevation of the production of ATP, and decreasing ROS production, as well as in reducing mitochondrial-endoplasmic reticulum Ca^{2+} transfer, preventing Ca^{2+} induced cell-death (Chen et al. 2005; Buck et al. 2016; Zhao et al. 2017; Jung et al. 2018). It also alleviates mitochondrial stress through contents fusion of partly damaged mitochondria with that of healthy ones. Both fission and fusion allow mitochondria in adapting to severe nutrient level changes allowing more metabolic flexibility. Most studies on mitochondrial dynamics suggest that maintenance of a balance between fusion and fission might prove to be more favourable for an organism to attain a healthier mitochondrial network than separately promoting or inhibiting either of the two processes (Sharma et al. 2019).

Both AMP-activated protein kinase (AMPK) and calcineurin-mediated extension of lifespan in *C. elegans* are suppressed by mitochondrial network fragmentation (Burkewitz et al. 2015). In addition, inactivating dynamin-related protein 1 (Drp1) in *C. elegans* was seen to significantly enhance the insulin signalling ability to extend lifespan, proposing a correlation between extension of lifespan and mitochondrial fusion/fission ratio (Yang et al. 2011). Therefore, it suggests that mitochondrial dynamics is involved in the regulation of ageing, along with or as a part of ageing-related pathways such as insulin and insulin/insulin-like growth factor-1 (IIS) signalling or AMPK pathway (Giorgi et al. 2018). In fungal models, *Podospora anserine* and *Saccharomyces cerevisiae*, deletion of dynamin-related protein 1 (Dnm1p), mediates fission and suppresses ageing, thereby extending lifespan (Scheckhuber et al. 2007). However, upregulating the expression of Drp1 in *Drosophila* during midlife have shown to extend lifespan, probably through autophagy (Rana et al. 2017). These studies suggest that there is no specific link between either fusion or fission and life expectancy, but rather the regulation of the mitochondrial quality control, controlled by fusion and fission,

which determines the process of ageing (Giorgi et al. 2018).

The occurrence of cardiovascular disease increases during ageing and is one of the main factors that ultimately lead to the death of an organism (Rapsomaniki et al. 2014). Hyperfragmented mitochondrial network and low expression level of optic atrophy 1 (Opa1) are associated with failure of the heart in human and mice (Chen et al. 2009). Opa1, along with the mitochondrial assembly regulatory factor (Marf, *Drosophila* mitofusin), are also necessary for the proper functioning of cardiomyocyte in *Drosophila* and defects in fusion are linked with cardiomyopathy (Dorn and Scorrano 2010). In mice, Opa1 unbalanced processing and decreased mitochondrial fusion are associated with fragmentation leading to heart failure (Wai et al. 2015). These studies show that fusion, along with Opa1, is essential for the proper functioning of the heart and prevents heart failure, and appear to be conserved throughout the three species, flies, mice and humans (Giorgi et al. 2018).

AD and PD are the most common age-related neurodegenerative diseases and have been associated to mitochondrial dynamics and mitophagy (Chen et al. 2009). In AD, amyloid- β ($\text{A}\beta$) is linked to hyperfragmentation of mitochondrial network induced by Drp1 in the disease progression (Reddy et al. 2017). Decreasing the Drp1 level also reduces the production level of soluble $\text{A}\beta$, protecting against mitochondrial and synaptic toxicities caused by $\text{A}\beta$ in the progression and pathogenesis of AD (Manczak et al. 2016). PD is also accompanied by fusion/fission ratio alterations. Fragmentation of the mitochondrial network and damaged anterograde axonal transport of mitochondria have been observed in the respiratory-chain deficient dopaminergic neurons (Sterky et al. 2011). Age-associated degenerative effects also affect muscles leading to muscle wasting. In aged mice, it was observed that the intermyofibrillar mitochondria in the skeletal muscle were longer and branched, indicating an increase of mitochondrial fusion and/ or a decrease of fission (Leduc-Gaudet et al. 2015). In case of human, aged subjects had lower Opa1 level in the muscle (Joseph et al. 2012).

Nutrient sensing association during ageing

Organisms are invariably dependent on their ability to utilize nutrients for growth and metabolic

functions. Multiple mechanisms and pathways respond to the level of nutrients in order to maintain homeostasis and disruption in these mechanisms disturbs the equilibrium of the cellular environment. These pathways exist in all living organisms, ranging from bacteria (prokaryotes) to yeast and mammals (eukaryotes). Such pathways respond to a range of nutrients and hormones to maintain coordination of coherent responses in the organism as a whole (Rosetti 2000). With an increase in age, many of the proteins involved in nutrient sensing are downregulated, and thus arises a need to actively explore these pathways in order to understand their mechanisms so as to delay the onset of metabolic disorders.

Some of the major pathways involved in nutrient sensing are insulin and insulin/insulin-like growth factor-1 (IGF-1) signalling (IIS) (Kaletsky and Murphy 2010), mechanistic target of rapamycin (mTOR) (Hansen et al. 2007), AMP-activated protein kinase (AMPK) (Greer et al. 2007) and sirtuins (Polito et al. 2010). When nutrients are available and stress levels are low, these pathways promote growth and reproduction. However, under low nutrient and high stress conditions, the pathways are altered, and as a consequence the cells are directed towards energy conservation and maintenance, implying that anabolism and catabolism of various metabolites are controlled by the nutrient sensing pathways. The nutrient-sensing pathways use post-translational phosphorylation and acetylation modification of proteins with modulation of gene expression to regulate energy homeostasis (Steinberg et al. 2009; Wellen et al. 2010; Imai et al. 2010). These pathways regulate several cellular processes such as protein synthesis, autophagy (Klionsky 2000), metabolism (Koubova and Guarente 2003), oxidative stress (Lou et al. 2017), immunity (Iyer et al. 2015) and reproduction (Templeman and Murphy 2018). The downstream signalling cascades of these pathways have been linked to extending lifespan in some lower organisms. These pathways cross-regulate each other, activating or inhibiting one another and their downstream targets. The genes coding for nutrient sensing proteins act as key regulators of lifespan and are also called “nutrient sensing longevity genes” (Mocchegiani 2016). Ageing and longevity are highly influenced by these conserved longevity pathways (Johnson et al. 2015).

IIS pathway

The IIS pathway is a cell-signalling pathway that responds to hormonal signals to control metabolism. It is activated by insulin and insulin-like peptide (ILP) ligands whose levels are responsive to nutrient availability and/or sensory information. It forms part of the somatotrophic axis consisting of growth hormone (GH), IGF-1, their receptors and its downstream signalling cascade. It is the most conserved nutrient sensing pathway in a wide spectrum of organisms (Kenyon 2005). The first evidence for its role in ageing was demonstrated in mutant *C. elegans* with mutations in *age-1*, phosphatidylinositol 3-kinase (PI3K), a downstream effector of insulin/insulin-like signalling; and *daf-2*, the insulin/insulin-like receptor (Freidman and Johnson 1988; Kenyon et al. 1993). It was later found that AGE-1, DAF-2 and DAF-16 are homologues of the human PI3K, insulin and IGF-1 transmembrane tyrosine kinase receptor and transcription factor, forkhead box O (FoxO), respectively (Kimura et al. 1997; Lin et al. 1997). Among IIS pathways multiple targets are protein kinase B (Akt), and RAS/MAPK pathway. Akt phosphorylates targets such as FoxO, causing its dispersal outside the nucleus, leading to a decrease in the transcription of its target genes (Siddle 2011). In mammals, Akt indirectly regulates TOR complexes by suppressing tuberous sclerosis complex (TSC) 1/TSC2 (Taniguchi et al. 2006). IIS stimulates the NF- κ B pathway, involved in immune-inflammatory processes (Gilmore and Wolenski 2012). IIS expands lifespan through modulating transcription factors like FoxO and heat shock transcription factor-1 (HSF-1) (Tullet et al. 2008).

In mammals, levels of IGF-1, predominantly produced by liver cells, are regulated by GH and a decline in the level of circulating IGF-1 and GH is associated with ageing (Sun et al. 2013). In long-lived dwarf Ames (*Prop1^{df}*) and Snell (*Pit^{dw}*) mice, decrease in levels of IIS is observed correlating it with longevity (Brown-Borg et al. 1996). It has been found that mice with deficiency of GH and reduced levels of IGF-1 demonstrate an increase in lifespan (Coschigano et al. 2000; Lorenzini et al. 2014). Similar observations on expansion of lifespan due to decrease in IIS has been found in *Drosophila* (Clancy et al. 2001). Consequently, mutations and downregulation of targets in these pathways have been associated with increased longevity (Hadem et al. 2020).

Among humans, various pockets of population like Ashkenazi Jewish centenarians and their Japanese peers have exhibited variants in the insulin receptor gene (Kojima et al. 2004; Suh et al. 2008). Moreover, predictions have been made about the relation between low IGF-1 levels and survival in humans with exceptional lifespan (Milman et al. 2014). Also, a deficiency in growth hormone receptors is linked to lower risk of age-associated conditions like cancer and diabetes, and a reduction in proteins that play a role in ageing (Guevara-Aguirre et al. 2011). Another study in Dutch nonagenarians also showed a positive correlation between IGF-1 and longevity (van der Spoel et al. 2015).

mTOR

The serine/threonine kinase, mTOR belongs to the phosphoinositide 3-kinase-related family that is highly conserved among eukaryotes and that can be inhibited by the immunosuppressive drug rapamycin (Sabatini et al. 1994). It plays an integral role in regulating growth and metabolism in response to several upstream cues, including signals from IIS and other growth factors, the cellular energy sensor AMPK, amino acids, lipids, cholesterol and oxygen levels (Saxton and Sabatini 2017). mTOR functions in two structurally and functionally distinct multiprotein complexes termed TOR complex 1 (mTORC1) and TOR complex 2 (mTORC2) (Loewith and Hall 2011). mTORC1, along with its downstream effectors ribosomal protein S6 kinase $\beta 1$ (S6K1) and eukaryotic translation initiation factor 4E(e1F4E)-binding protein 1(4E-BP), plays a major role in nutrient sensing by regulating cell growth (accumulation of cell mass) through coordination of protein anabolism (Ma and Blenis 2009), glycolysis (Shi et al. 2018), autophagy (Ganley et al. 2009; Kim et al. 2011) promoting lipid and nucleotide synthesis (Ben-Sahra et al. 2013) modulation of the senescence-associated secretory phenotype (Laberge et al. 2015).

mTORC1 activity increases during ageing contributing to age-related obesity supporting the idea that intense anabolic activity is responsible for accelerating ageing and age-related diseases (Yang et al. 2012). Enhanced 4E-BP increases translation of peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α), increasing mitochondrial respiration and inhibiting autophagy, thereby accelerating ageing

(Tsai et al. 2015). However, various studies have shown that the mTOR pathway regulates lifespan in simple organisms such as yeast, worms and flies where mTORC1 was inhibited (Vellai et al. 2003; Kapahi et al. 2004; Kaerberlin et al. 2005; Arriola Apelo and Lamming 2016). The mTOR complexes are inhibited by rapamycin and rapalogs. Rapamycin, an immunosuppressive, anti-fungal drug inhibits mTORC1, by forming a complex by binding with the small endogenous protein FK506-binding protein (FKBP) and inhibiting mTORC1 (Shimobayashi and Hall 2014). mTORC1 activity is reduced in vital organs of Snell dwarf and global GH receptor (GHR) gene-disrupted mice (Dominick et al. 2015). In elder humans, the inhibition of mTOR has led to improvement in immunosence and immune functions (Manick et al. 2014).

mTORC2 controls growth by regulating lipogenesis, glucose metabolism (García-Martínez and Alessi 2008; Yuan et al. 2012) and the actin cytoskeleton (Cybulski and Hall 2009). In mammals, an interaction between mTOR and IIS signalling occurs via Akt, as it gets activated upon phosphorylation by mTORC2 (Sarbasov et al. 2005) leading to inhibition of Foxo transcription factors (Guertin et al. 2006). mTORC2 is also inhibited upon long exposure to rapamycin (Sarbasov et al. 2006). Although not much is known about the role of mTORC2 in ageing, but in some studies it was found that inhibiting mTORC2 may play a role in extending lifespan (Yu et al. 2019). In male mice, pharmaceutical treatment with acarbose and 17 α -estradiol extends lifespan due to a boost in hepatic mTORC2 signalling (Garatt et al. 2017).

AMPK

A critical sensor of energy status is AMPK, which is activated in response to cellular energy depletion. AMPK is activated by direct AMP binding or due to elevated cellular levels of AMP, ADP, and/or calcium (Hardie et al. 2012, 2016). It is a key regulator of energy homeostasis and mitochondrial metabolism (Herzig and Shaw 2018). AMPK is a heterotrimeric kinase composed of one catalytic subunit α and two regulatory subunits β and γ (Steinberg and Kemp 2009). The catalytic α -subunit contains an important residue, Thr-172 located in the N-terminus of the kinase domain (Hawley et al. 1996). In mammals, AMPK is activated by upstream kinases, liver kinase

B1 (LKB1) (Woods et al. 2003; Shaw et al. 2004) and calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) in response to intracellular Ca^{2+} (Hurley et al. 2005).

Under prolonged conditions of reduced energy, AMPK phosphorylates PGC-1 α , class IIA histone deacetylases (HDACs) co-activating cAMP response element-binding protein (CREB), CREB-regulated transcription coactivator-2 (CRTC2) and FoxO pathways. AMPK activates processes that results in breakdown of nutrients and produces energy by activating the uptake of glucose and fatty acids. AMPK reprogrammes metabolism through transcriptional regulation of biosynthetic pathways and use of mitochondrial substrates as an energy source (Mihaylova and Shaw 2011). AMPK controls metabolism at the transcriptional level by phosphorylating sterol regulatory element-binding protein 1 (SREBP1) (Li et al. 2011), carbohydrate-responsive element-binding protein (ChREBP) (Kawaguchi et al. 2002) and hepatocyte nuclear factor 4 α (HNF4 α) (Hong et al. 2003) which are key transcriptional regulators of lipid and glucose metabolism. AMPK activates autophagy by inhibiting mTORC1 indirectly by activating TSC2 and rapTOR (Inoki et al. 2003; Gwinn et al. response pathways like AMPK, SIRT).

AMPK plays a role in increasing healthspan by regulating inflammation by inhibiting a pro-inflammatory transcription factor NF- κ B through its downstream signalling cascade like SIRT1, PGC-1 α , p53, and Forkhead box O (FoxO) factors (Salminen et al. 2011). AMPK extends lifespan by activating ULK1, a kinase needed for autophagy and suppressing mTOR (Kim et al. 2011). The activation of AMPK has been found to be beneficial in age-related pathologies like atherosclerosis, T2DM, obesity and other metabolic diseases (Day et al. 2017). The role of AMPK in lifespan expansion by anti-ageing small molecules like metformin, resveratrol, aspirin and rapamycin has also been established as reviewed elsewhere (Burkewitz et al. 2014).

Sirtuins

Another class of energy sensors are sirtuins, a family of NAD⁺-dependent enzymes that catalyze post-translational modification of both histone and non-histone proteins. Since sirtuins are dependent on NAD⁺ for its activity, they are activated during the

state of fasting or exercise. Sirtuins comprise a universally conserved family of NAD⁺-dependent deacetylases and/or ADP-ribosyltransferases found in all three domains of life (Frye 2000; Imai et al. 2000; Landry et al. 2000). Sirtuins regulate energy metabolism and are modulated by diet. In mammals, the family is represented by seven member SIRT1-7, variably located in different cellular compartments like nucleus (SIRT1,2,6,7), mitochondria (SIRT 3,4,5), cytoplasm (SIRT 1,2) (Frye 2000). Its targets for deacetylation include p53, NF- κ B, PGC-1 α , eNOS, mTORC2 and FoxO3a.

SIRT1 is the most studied among its counterparts. SIRT1 deacetylates many of the proteins and enzymes involved in metabolic processes (Zhao et al. 2010). SIRT1 regulates gluconeogenesis and glycolysis via PGC-1 α by promoting its nuclear localization, in laboratory animals and in vitro (Nemoto et al. 2005). In addition, it inhibits glycolysis while activating gluconeogenesis and fatty acid oxidation in most tissues (Silva and Wahlestedt 2010). PGC-1 α lies at the center of the energy sensing pathway as it is phosphorylated and deacetylated by both AMPK and sirtuins, respectively and is a key controller of transcription factors to activate gene expression and control mitochondrial biogenesis (Rodgers et al. 2005). Sirtuins play a role in a number of age-related degenerative conditions like cardiovascular diseases, neurodegenerative diseases, cancer and diabetes and can serve as a therapeutic target (Hall et al. 2013).

Sirtuins role in lifespan extension was only discovered due to overexpression of Sir2 genes in *C.elegans* (Tissenbaum and Guarente 2001). In mice, the role of sirtuins in longevity has been much explored. Overexpression of Sirt1 in transgenic mice showed features resembling calorie restricted mice like lean body, reduced blood cholesterol levels and metabolically active (Bordone et al. 2007). On the other hand, a high fat diet led to loss of Sirt1 in adipose tissues in mice (Chalkiadaki and Guarente 2012). In humans, undergoing dietary restriction the levels of SIRT1 increases in the muscles (Civitarese et al. 2007). Sirt3 is required for the reduction of oxidative damage in cochlear cell in calorie restricted mice (Someya et al. 2010).

There is an important correlation between the nutrient and energy sensors. The energy sensors (AMPK and Sirtuins) function in the opposite direction of nutrient sensors (mTOR). Overall, AMPK and

sirtuins regulate the catabolism of metabolites and inhibit their anabolism. These signalling pathways are interconnected as they regulate each other by its downstream signalling cascades. Energy sensors play a central role in the metabolism of glucose, lipid, protein and lastly autophagy and mitochondrial homeostasis (Guarente 2011; Houtkeeper et al. 2012; Herzig and Shaw 2018). It has been found that the upregulation of these pathways aids towards healthy ageing.

Metabolic dysfunctions associated with mitochondrial and nutrient sensing deregulation

Visceral fat accumulation or obesity during ageing poses higher risk of morbidity due to surge in possible risk for cardiovascular diseases, T2DM and hypertension. In obesity-associated diseases like T2DM and insulin resistance, lesser expression of mtDNA and reduced levels of mitochondrial complexes have been observed, indicating dysfunction of mitochondria. This affects organs such as liver, muscle and adipose tissue, thereby developing metabolic disorders (Patti and Corvera 2010). Fatty acid oxidation capacity is also reduced due to mitochondrial dysfunction and has been proposed to induce liver, muscle and adipose tissue to accumulate lipids, particularly long-chain fatty acids, which increases resistance to insulin (Lowell and Shulman 2005; Hafizi Abu Bakar et al. 2015). Increased level of ROS has been observed in skeletal muscle of obese individuals due to the accumulation of impaired mitochondria during ageing, leading to muscle deterioration (Barbieri et al. 2013). Mitochondrial network fragmentation and reduction in the mitochondrial membrane potential has been linked to reduced mitofusin 2 (Mfn2) expression in the skeletal muscle of obese individuals and in T2DM patients. Mitofusin proteins are located on the surface of the outer mitochondrial membrane and act in the membrane fusion process of mitochondria. The reduced expression of Mfn2 plays a crucial role in the impairment of mitochondria linked with accumulation of fat (López-Lluch et al. 2018).

In the white adipose tissue, AMPK, among the several metabolic regulators, has a critical role in metabolic syndrome progression and resistance to insulin. Various downstream substrates required for the increase in oxidation of lipids and glucose uptake

are regulated by phosphorylated AMPK, thereby resulting in glucose intolerance, obesity and lower physical capability in case of insufficient AMPK (Steinberg et al. 2010). As regards to its crucial role in regulating metabolism and mitochondrial activity, a decline in AMPK levels and activity during ageing can lead to physiological decline of adipose and other tissues in old age (Ruiz et al. 2016).

Regulation of mitochondrial physiology by nutrient sensors

Mitochondrial activity, dynamics, biogenesis and turnover respond to nutrient availability i.e., nutrient excess stimulates fission and nutrient deficiency stimulates fusion (Rambold et al. 2011). It is regulated by nutrient sensors such as mTOR, AMPK and sirtuins, maintaining an equilibrium of activity according to the requirement of the cells (López-Lluch 2017). During ageing, an imbalance in this process contributes to the loss of mitochondrial homeostasis in sarcopenic muscles, associated with the upregulation of mitochondrial fusion in skeletal muscle (Joseph et al. 2013).

In conditions of high calorie consumption, there is activation of mTOR. Various cellular processes—insulin resistance, adipogenesis, inflammation, tumor formation and angiogenesis also play a role in the activation of mTOR (Lee et al. 2007; Laplante and Sabatini 2009). mTOR signalling pathway is downregulated by AMPK, thereby regulating cell bioenergetics, and sirtuins are activated in conditions when there is low amount of energy such as calorie restriction (CR) (López-Lluch et al. 2018). Mitophagy, essential for cell survival is regulated by AMPK, mTOR and FoxO3 transcription factors (Zhao et al. 2007; Hirota et al. 2012). Downregulation of mTOR stimulates mitophagy and upregulation of AMPK activates mitochondrial biogenesis, oxidative metabolism, and resistance to oxidative stress (Guarente 2014). By modulating autophagy and mitophagy, mTORC1 regulates mitochondrial turnover. Through the phosphorylation of inhibitory sites of initial mediators unc-51-like kinase 1/2 (ULK-1 and ULK-2), mTORC1 blocks autophagy, while it is induced by AMPK by phosphorylating the activation sites of the same initiators (Akers et al. 2012).

A metabolic shift to β -oxidation, lower respiration rate, and more OXPHOS proteins were found in Ames dwarf and GH deficient mice, linking IIS signalling and mitochondrial metabolism (Brown-Borg et al. 2012). The expression of genes involved in mitochondrial processes like β -oxidation, TCA cycle and glycolysis were found to be higher in Fat-specific insulin receptor knockout mice (FIRKO) with respect to the control mice of same age (Katic et al. 2007), implying the role of IIS signalling and somatotropic axis in mitochondrial metabolism.

Sirtuins are associated to different important features of cell physiology, from the control of cell cycle to metabolism and antioxidant defense. Their effect on the physiology of mitochondria and metabolism of cell has been linked to their impact on extension of lifespan. Sirtuins activation and mitochondrial biogenesis helps in part of the overall effect of CR (Guarente 2013). The aforesaid nutrient sensors also regulate the activity of the crucial transcription factor, PGC1 α , involved in the activation of mitochondrial biogenesis. PGC1 α modulates mitochondrial biogenesis and oxidative phosphorylation, balances mitochondrial dynamics, and controls the copy number of the mitochondrial genome (Gouspillou et al. 2014). It also controls the expression of transcription factors involved in mitochondrial biogenesis and respiration control, like the nuclear respiratory factors 1 and 2 (NRF1 and 2), mitochondrial transcription factor A (TFAM) or peroxisome-proliferator activated receptor- γ (PPAR γ) (Martin-Montalvo and de Cabo 2013). SIRT3, present in mitochondria having deacetylase activity, is stimulated after CR in the skeletal muscle and under a high-fat diet, its level decreases suggesting a calorie-dependent modulation (Palacios et al. 2009). It takes part in the breaking down of lipids and regulation of complexes II, III and IV activities of the ETC by deacetylation. It is also involved in the modulation of autophagy by FoxO3, regulation of Mn-SOD activity and mitochondrial dynamics through autosomal dominant optic atrophy-1 (OPA1) activation (López-Lluch et al. 2018). FoxO proteins take part in the removal of mitochondria and are involved in modulating cell inducing several stress-induced genes. Preventing mitochondrial dysfunction and improving mitochondrial functional quality by CR, polyphenols or exercise are associated with FoxO proteins regulation during

ageing and their modulation by mTOR, AMPK and sirtuins (López-Lluch and Navas 2016).

Sestrins, a highly conserved stress-inducible small protein, regulate mTORC1 activity through the activation of AMPK. Inactivation of sestrin gene expression, in invertebrates, gives rise to various metabolic dysfunctions such as oxidative damage, mitochondrial dysfunction, accumulation of fat and deterioration of muscle favouring the acceleration of ageing (Lee et al. 2013). Sestrins have been linked to ageing through their effect on the rate of mitochondrial turnover (Wang et al. 2017). They are also associated with the metabolic regulation in mice aiding longevity effect. Sestrin proteins are regulated by oxidative stress through p53, NRF-2, AP-1 and FoxO and they modulate various components that help in decreasing the production of ROS, inducing mitochondrial biogenesis and mitophagy, thereby ameliorating oxidative metabolism (Lee et al. 2013). Through activating AMPK, the inactivation of sestrins-dependent mTORC1 plays a key role in maintaining autophagy and in defective mitochondria elimination (Ishihara et al. 2013). The levels of sestrins in muscle decline during ageing, but the level of sestrin 2 increases in mouse muscle in response to insulin and autophagy (Lenhare et al. 2017). Modulated by a number of stress factors, sestrins family of proteins, are emerging as essential metabolic regulators for mitochondrial turnover and various age-related complications by hormetic response to a mild stress (Wang et al. 2017).

Improving healthspan through dietary interventions

Impaired mitochondrial function and nutrient sensing are the common denominator in age-related fat accumulation leading to metabolic dysfunction. It can be said that the contribution of these processes is the major contributors in pathogenesis of age-related diseases. Over the period of a century, various methods have been used to alleviate the effects of ageing. Dietary interventions like calorie restriction (CR), intermittent fasting (IF), physical exercise, and the use of certain chemical/nutraceutical agents referred to as CR mimetics, are known to alleviate the effects of ageing. Several studies have shown that CR increases the capacity to extend longevity, affecting both,

median and maximum lifespan in different organisms from yeasts to mammals (Sharma 2004; Testa et al. 2014, Madeo et al. 2015). CR is a nutritional intervention where one is subjected to a reduced calorie intake without resulting into malnutrition. Different kinds of dietary interventions regimens are followed in studies to analyse and understand the effects in various animal models as per their lifespan. There is also variation in the duration of the time followed for the regimen. These include calorie restriction (CR), intermittent fasting (IF) or alternate day fasting, ketogenic diet (KD), time restricted feeding (TRF) and diet with specific amount of limited nutrients.

Calorie restriction

CR is a dietary restriction regimen where there is a 10–50% decrease in the overall calorie intake without malnutrition for a particular duration. CR increases lifespan when calories are limited by a certain proportion but can have deleterious effect when the restriction percentage is increased beyond 50%. Variations in the effects of CR on ageing have been reported depending on the time of initiation, dietary composition, the duration of regimen, sex and species (Weindruch and Sohal 1997). CR has shown to have varying effects on different tissues (Arslan-Ergul et al. 2016).

The beneficial of CR are modulated through the mechanisms of nutrient sensing pathways and functions of mitochondria. Reducing oxidative stress is one of the major effects of CR on cellular physiology. This can be attained through various mechanisms, including a reduction in the rate of ROS generation, upregulation in the removal of ROS, thereby minimizing their harmful effects, and stimulating the repair process to lessen the impact of the damages. Various studies have shown that CR regulates redox homeostasis through these mentioned processes. There is also a lesser production of superoxide radical generation by CR (Speakman and Mitchell 2011).

CR helps in removing visceral fats, which is harmful due to its pro-inflammatory and diabetogenic activity, for healthy ageing (Finkel 2015). It also induces autophagy in human tissues, providing various anti-ageing effects by stimulation of better-quality control on organelles, stem cell optimum activity promotion, amelioration of immunological activities, and malignant transformation prevention

(Galluzzi et al. 2015). Efficient autophagic reaction also improves various features of disorders associated with ageing, such as neurodegeneration, T2DM and arteriosclerosis (Levine and Kroemer 2008). CR activates autophagic responses through nutrient sensors such as SIRT1, AMPK, and mTORC1 and combines such responses to FoxO1 activation, which maintains telomerase activity as well (Makino et al. 2016).

Intermittent fasting

IF is a dietary restriction regime in which organisms undergo long hours of fasting and refeeding that progressively reduces the total food intake by roughly 30% in model organisms (Suchiang and Sharma 2011). It has served as one of the alternatives for traditional CR. There are various modifications of IF including 12 h eating and 12 h fasting, alternate day feeding, 5:2 IF (5 days eating followed by 2 days fasting in a week). IF resembles the prehistoric times, where food was scarce, and the organisms needed to starve until food was available. IF in mice reduces inflammation and enhances autophagy by the activation of transcriptional factors induced by nutrient and hormonal signals (Yang et al. 2016; Bagherniya et al. 2018). IF also enhances long-term memory consolidation and improves physiological health (Dias et al. 2021; Zhang et al. 2022). IF upregulates brain-derived neurotrophic factor (Bdnf) expression in various brain regions of rodents (Mattson and Arumugam 2018; Liu et al. 2019). This can possibly regulate systemic and local anti-ageing effects as Bdnf stimulates synaptic plasticity, enhances neurogenesis, promotes neurons' resistance to cell death, modulates appetite, improves cardiovascular and gastrointestinal autonomic control systems, and elevates glucose metabolism. In addition, IF alleviates various organs from ischemic damage, delays neurodegeneration in several rodent models, and counteracts or improves the after-effect of epileptic seizures and neuro-trauma (Longo and Mattson 2014; López-Otín et al. 2016). IF shows similar effects in humans in other age-related diseases (de Cabo and Mattson 2019).

Time restricted feeding

In TRF, the organisms are allowed to feed *ad libitum* during a limited period of 8 h and fasted for the next 16 h. This cycle of feeding and fasting continues for

a longer duration in order to determine its impact on the organism. The concept of TRF arose within the context of circadian rhythms. In mice, TRF reduces adiposity and pro-inflammatory cytokines (Sundaram and Yan 2016), improves insulin resistance and hepatic steatosis (Ryan et al. 2013), gives protection against obesity, fatty liver disease, insulin resistance, hyperinsulinaemia and inflammation (Hatori et al. 2012). These positive metabolic effects are mediated by metabolic modulation of mTOR, CREB and AMPK pathway (Chaix et al. 2014). Recent TRF trials in humans have allowed a feeding window between 4 and 12 h, although a window of <10 h is thought to be optimal based on glycogenolysis, fatty acid oxidation, and gluconeogenesis modulations occurring in the absence of dietary glucose availability. In a recent study where sedentary adults with overweight and obesity restricted their eating to an 8-hour *ad libitum* flexible feeding window; study volunteers experienced significant weight reduction (Anton et al. 2019).

Ketogenic diet

KD is a dietary regimen, which represents a group of diets, comprising of high fat and low carbohydrate content. After the application of a KD the body switches into starvation mode. In this situation the body uses fat as the energy source, and produces ketones- β -hydroxybutyrate, acetoacetate and acetone. Ketone bodies are lipid driven molecules (beta-oxidation), and they act as alternative substrates for energy production during fasting and low-carb diets (Jensen et al. 2020). In KD fed mice, the cardiac cells were found to abate oxidative stress, improve mitochondrial function and promote autophagic flux (Yu et al. 2020). KD improves mitochondrial biogenesis via the PGC-1 α -Sirt3-UCP2 axis (Hasan-Olive et al. 2019) and protein acetylation levels and regulated mTORC1 signalling, demonstrating that KD extends longevity and healthspan in mice (Roberts et al. 2017). Also in rats, KDs change the gene expression levels in the CA3 region of hippocampus, which is known to impact cognitive abilities during brain ageing (Hernandez et al. 2019). These data suggest that KDs have the potential to impact the ageing.

Diet with limited amount of specific nutrients

The alternative to aforesaid dietary interventions is also gaining popularity as these effects seem to have a temporal impact on the organisms (Austad and Hoffman 2021). The idea that nutrients and not calories were responsible for the beneficial effects of dietary restriction has also been studied. Restriction of specific components like proteins or rather specific amino acids have also shown to impart similar results independent of CR (Soultoukis and Patridge 2016). Diets restricted with essential amino acids like methionine, tryptophan or threonine and other branched chained amino acids (BCAAs) like leucine, isoleucine and valine have also been studied in model organisms (Xiao et al. 2011; Perrone et al. 2013; Fontana et al. 2016). Such diets also impart its effects via the nutrient sensing proteins like mTOR, AMPK and GCN2.

CR Mimetics

The implementation of such dietary interventions in humans comes with some side effects like lowering of body temperature and a decrease in circulating sex hormones (Cangemi et al. 2010; Soare et al. 2011) and/or slow wound healing (Hunt et al. 2012). This led to the development of a newer strategy as CR mimetics. CR mimetics (CRM) is defined as substances that mimic the metabolic, hormonal and physiological effects of CR (Ingram and Roth 2015). In principle, a successful CRM would increase healthspan and lifespan by targeting the metabolic and stress response pathways affected by CR, but without markedly restricting caloric intake. Interestingly, some of the known CR mimetics compounds like resveratrol and metformin act as activators of energy sensors (AMPK and sirtuins) or drugs like Rapamycin inhibit the nutrient sensor mTOR.

Various other compounds also act as CR mimetics and help to increase healthspan in humans. Polyphenolic compounds, such as curcumin and resveratrol, and nutritional mushrooms like *Coriolus versicolor* and *Hericium* have strong redox-active properties which when ingested in small doses were found to be non-toxic in numerous experimental models, including humans. However, at high concentrations, these compounds exhibited toxic properties, which are

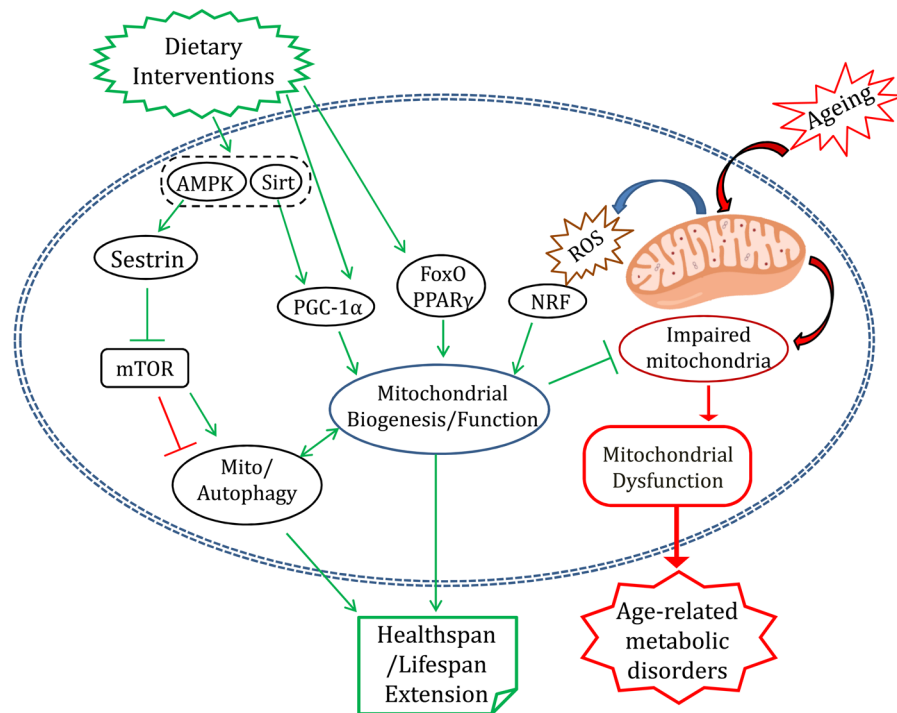


Fig. 1 An overview of mitochondrial regulation by nutrient sensors. Various nutrient sensors regulate mitochondrial biogenesis, function and mito/autophagy to avoid the accumulation of impaired mitochondria. Impaired mitochondria accumulation is one of the main factors for mitochondrial dysfunction during ageing, resulting in a number of age-related metabolic disorders. Interventions such as CR and CR

mimetics help in alleviating the ill-effects of dysfunctional mitochondria by stimulating mitochondrial biogenesis and mito/autophagy. [AMPK, AMP-activated protein kinase; Sirt, sirtuins; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1 α ; NRF, nuclear respiratory factors; PPAR γ , peroxisome-proliferator activated receptor- γ ; FoxO, forkhead box O; mTOR, mechanistic target of rapamycin]

harmful to the organism, thereby showing biphasic dose response when ingested in hormetic range (Calabrese et al. 2010; Trovato et al. 2018). These nutraceuticals induce adaptive cellular stress response pathways like AMPK, SIRT, FoxO, PGC1 α , Nrf2, antioxidant response elements (AREs) and heat shock response (HSR) (Calabrese et al. 2010; Martel et al. 2019). Activation of the Nrf2/ARE and HSR together reduces amyloid formation in AD, induces cytoprotective enzyme heme oxygenase 1(HO-1) and mediates anti-inflammatory effects via the downregulation of nuclear factor kappa B (NF- κ B), thereby, inducing protection against oxidative stresses that cause a wide range of chronic pathologies, including neurodegenerative conditions (Yang et al. 2005; Calabrese et al. 2010; Miquel et al. 2018). Across species, the longevity network detects nutrient availability and energy status, mitochondrial functional status and the production rate of ROS in the mitochondria for

the regulation of lifespan, by coordinating the information with various signalling pathways, including the vitagenes. Vitagenes encode for genes, viz. heat shock proteins (Hsp) Hsp32, Hsp 70, the thioredoxin and the sirtuin protein systems that are involved in regulating cellular homeostasis (Calabrese et al. 2012). Activation of the vitagenes through hormetic CR-mimetics produces molecules like heat shock proteins, glutathione and bilirubin, having anti-oxidative and anti-apoptotic activities (Mancuso et al. 2006; Calabrese et al. 2007, 2010; Cornelius et al. 2013).

Conclusions

The intricacy of ageing process is highly complex and can only be understood upon analyzing its various aspects in a biological network. In the course of ageing, the role of mitochondria is regulated by various

nutrient sensors directly, as these sensors control mitochondrial functions such as biogenesis, oxidative phosphorylation, autophagy, and mitochondrial turnover. Nutrient sensors such as mTOR, AMPK and sirtuins influence the expression of their downstream target transcription factors to reprogramme the signalling network and change the machinery and metabolism of the cell (Fig. 1). The identification of both deregulated nutrient sensing and mitochondrial dysfunction as network hallmark of ageing, opens up new avenues in future research in the area of biomedical gerontology. These processes are interdependent and form a network that regulates cellular metabolism and homeostasis during ageing. However, the core idea of all ageing research is to attain longevity with an extended healthspan. Also, nutrition serves as the most convenient way to act upon ageing. Dietary interventions act upon both these processes maintaining the metabolic homeostasis as a result of hormetic response by various signalling pathways and reducing the generation of ROS. Thus, it may prove to be effective in delaying the onset of age-related disorders. A big challenge that lies ahead of researchers is to find out the effect of the various interventions on different individuals and the optimum level of intervention to be followed to attain the goal of extended healthspan and lifespan in humans.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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