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Sirtuin-Dependent Metabolic Control and Its Role in the Aging Process

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1. Introduction

During last years, the protein family of sirtuins, composed by NAD^+-dependent deacetylases, has emerged as a key factor in aging. From yeast to humans, sirtuins are involved in metabolic changes that induce a higher respiratory capacity accompanied by lower oxidative damage. They are involved in the control of glucose catabolism, fatty acid metabolism, respiratory chain activity in mitochondria and several other metabolic processes including control of antioxidant capacity in cells and tissues (Dali-Youcef et al., 2007; Elliott & Jirousek, 2008; Lomb et al., 2010; Pallas et al., 2008).

As these deacetylases are dependent on the NAD^+/NADH ratio, they can be considered as important sensors of the metabolic status of the cells and probably because this they are one of the main family of proteins involved in the regulation of metabolism in the cell (Li & Kazgan, 2011). Further, their relationship with the AMPK-dependent pathway, that controls respiratory metabolism by inhibiting insulin-dependent signaling, highlights the importance of these proteins in metabolic regulation and especially in insulin-resistance, diabetes and obesity (Canto et al., 2009; Ruderman et al., 2010).

Sirtuins have been involved in aging process and considered important factors in delaying aging process and increase longevity (Guarente, 2000; Tissenbaum & Guarente, 2001). However, very recent studies have questioned the role of these deacetylases in longevity (Burnett et al., 2011; Viswanathan & Guarente, 2011). But their activity in yeast, worms and flies still permits to correlate its function in metabolism and dietary-dependent modulations with aging process (Guarente, 2008). However, to date, in mammals and, especially in humans, their role in longevity is not clear. Whereas in lower organisms only one member has been found, SIR2, in mammals, seven members have been described to date. This fact indicates a higher complexity in interactions, targets and functions in higher animals than in lowers. Further, in mammals, the specific distribution of these deacetylases among the different cell compartments also indicates several local-dependent influences of sirtuins.

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Aging can be considered a severe deleterious process that affects all the compartments in cells and also all the tissues and organs in the organism. Apart of the different theories of aging (Jin, 2010), the main common factor is the accumulation of non-metabolizable or degradable molecules into cells and tissues that impair their correct function. In few words, we age because our organism accumulates rubbish and we are unable to eliminate or recycle it. Most of the damaged molecules are the result of a unbalanced metabolism that produces high levels of reactive molecules accompanied by a low capacity of the endogenous antioxidant mechanisms of cells and the recycling mechanisms such as proteasome and autophagy or DNA-damage reparation (Asha Devi, 2009; Fleming & Bensch, 1991; Maynard et al., 2009; Perez et al., 2009; Sohal et al., 1994). As results, oxidized molecules accumulate into cells impairing their physiology at all levels. Then, a balanced and controlled metabolism will improve oxidant/antioxidant relationship and delay the accumulation of oxidized molecules in aged cells and tissues.

The present chapter is focused on the role of the metabolism in aging process and the importance of sirtuins in its control. We will describe the different pathways regulated by sirtuins and how modifications in NAD^+/NADH ratio can affect the activity of these deacetylases. Moreover, we will discuss the possible role of NADH-dependent oxidoreductases in the control of metabolism through these proteins. Furthermore, the role of a known polyphenol, resveratrol, as agonist of sirtuins and caloric restriction in aging and metabolic control will be also revised.

2. Sirtuins, a heterogeneous family of protein deacetylases

Sirtuins are a family of proteins that share a conserved NAD^+-dependent acetyl-lysine deacetylase and ADP-ribosyltransferase activity. They have been related to the regulation of the metabolism and also lifespan being involved in cell survival and apoptosis, cell proliferation and senescence. They are widely located in all the organs and near all the subcellular locations. The seven isoforms found to date in humans localize either in the nucleus, cytoplasm or mitochondria. The use of modified organisms showing increasing gene dosage of sirtuin orthologs in eukaryotes such as yeast, worms or flies have demonstrated that these enzymes are directly involved in lengthening of longevity (Guarente, 2007). Further, the relationship between calorie restriction and longevity indicate that metabolism is directly involved in aging, and then, as sirtuins are involved in the control of metabolism, a direct link between the activity and modulation of these proteins and a longer lifespan seems to be convincing (Balcerczyk & Pirola, 2010).

In contrast with class I, II and IV deacetylases, mainly involved in the control of epigenetic processes (Kuzmichev & Reinberg, 2001), sirtuins are members of the class III characterized to be dependent on NAD^+. These enzymes catalyze the reaction shown in figure 1. They bind to a Nε-acetyl-lysines of the target protein and deacetylate them by using NAD^+ as substrate and producing nicotinamide (NAM) and 2′-O-acetyl-ribose (2′-O-AADPR) as products (Hirsch & Zheng, 2011). In this process, increasing levels of NAD^+ increase the activity of sirtuins whereas higher NAM or NADH levels exert an inhibitory effect (Wolberger, 2007). Further, the expression of sirtuins are also regulated by the ratio NAD^+/NADH since higher mRNA levels have been found when NADH/NAD^+ levels rise (Gambini et al., 2011). Then, they can be considered as metabolic sensors since they can modulate their activity and levels depending on the ratio NAD^+/NADH.

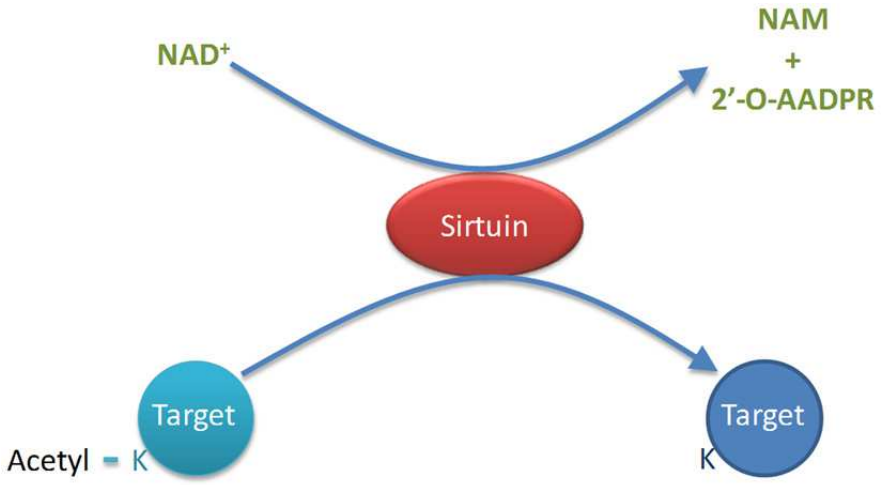

Fig. 1. Deacetylation of K-acetyl residues in targets of sirtuins.

The first member of this family studied in deep was the yeast Sir2. This deacetylase is responsible of silencing chromatin by deacetylation of histones (Blander & Guarente, 2004) and has been related to the increase in longevity in yeast, worms and flies. Apart of its activity reducing the accumulation of chromatin of ribosomal RNA (rRNA) genes in yeast, the prolongevity of Sir2 has been also related to the modulation of mitochondrial function providing benefit to slow aging and associated diseases (Guarente, 2008).

To date, seven sirtuins have been described in mammals. They are designed as SIRT1 through SIRT7. Based on the homology of the 250 aminoacids core domain, the mitochondrial SIRT3, the nuclear-cytosolic SIRT1 and the mainly nuclear SIRT2 show the closest homology to yeast SIR2 (Frye, 2000). However, if we attend to the alignment of the aminoacid sequence of the human members we can see that the identity at the aminoacid sequence is very low among the members of sirtuins family (Table 1) and only deacetylase sirtuin-type domain shows some homology being highly in the NAD^+-binding and in the catalytic domains (Figure 2). A possible explanation for these high differences in sequence between the members of sirtuin family in mammals can be found in the plethora of targets that can be recognized by the different members of the family and in their different and selective locations into the cell.

	hSIRT1	hSIRT2	hSIRT3	hSIRT4	hSIRT5	hSIRT6	hSIRT7
hSIRT1	100						
hSIRT2	34.34	100					
hSIRT3	30.94	44.85	100				
hSIRT4	24.55	21.88	26.02	100			
hSIRT5	25.63	22.71	27.66	27.13	100		
hSIRT6	21.56	24.21	28.84	28.43	20.59	100	
hSIRT7	20.97	22.28	23.70	28.14	22.01	36.77	100

Table 1. Pairwise comparison of aminoacid sequences from the human sirtuin members. From BLAST (basic local alignment search tool) analysis of the indicated proteins in figure 2.

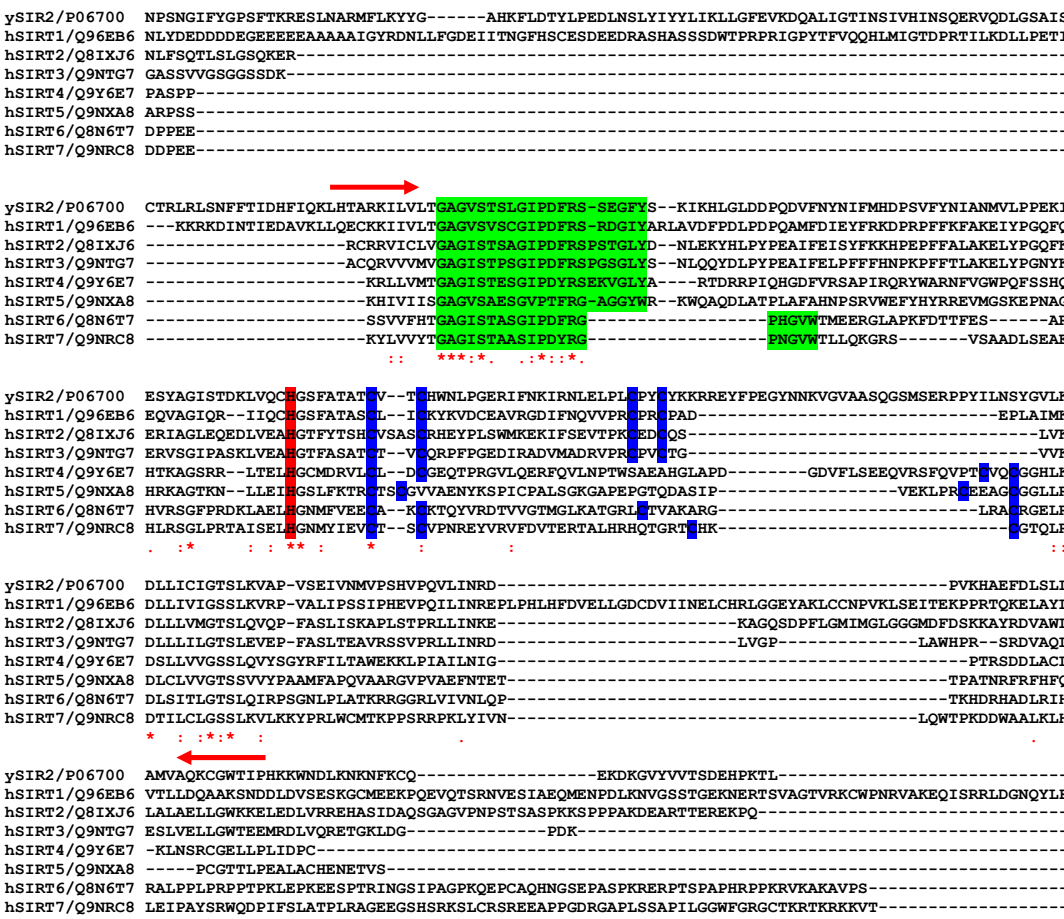

Fig. 2. Alignment of centre core of human sirtuins family in comparison with yeast sir2 (previous page). The figure represent Clustalw alignment from indicated yeast and human sirtuins indicated by their UniProtKB accession numbers. In yeast sir2, the deacetylase sirtuin-type dominium is from 245 to 529 (red arrow) that correspond with the highest homology sequence among the members of the family. The NAD^+ binding domains are indicated in green, there are the most conserved domains in the whole family. The active site is determined by a histidine at 364 position of sir2 that acts as a proton acceptor, the key histidines in other members have been determined in silico by homology. Although it has been indicated that these enzymes do not bind zinc, probable cystein residues able to bind zinc are also conserved in some of the members of the family (in blue). Regarding regulation, in sir2 two points of regulation by phosphorylation, phosphorylation at serine 23 and at tyrosine 400 have been determined (violet residues). None of them are conserved residues in human sirt forms. Further, in SIRT1, modifications at cysteines 395 and 398 by s-nitrosylation impede the binding of NAD^+ and then, the activity of the enzyme.

	S. cerev. SIR2	S. pombe SIR2	D. melanog. SIR2.1	C. elegans SIR2	D. rerio SIR2	M. musc. SIRT1	H. sapiens SIRT1
S. cerev. SIR2	100	41	43	39	45	40	40

Table 2. Pairwise comparison of the aminoacid sequences among yeast (*Saccharomyces cerevisiae*) SIR2 and higher homologues in model animals: fission yeast (Saccharomyces pombe); fly (*Drosophila melanogaster*); worm (*Caenorhabditis elegans*); zebrafish (*Dario rerio*); mice (*Mus musculus*) and human (*Homo sapiens*). The percentage of identity in comparison with *S. cerevisiae* sir2 protein is indicated. From BLAST analysis of the indicated proteins.

Among the other human sirtuins, SIRT4 and SIRT5 are mitochondrial sirtuins that show predominant ADP-ribosyl-transferase activity and a weak deacetylase activity and are involved in urea cycle regulation (Nakagawa & Guarente, 2009). On the other hand, SIRT6 and SIRT7 are considered as members of another subclass of sirtuins involved in reparation of DNA and the control of ribosomal RNA production through cell cycle (Lombard et al., 2008).
Although it has been described that sirtuins does not bind zinc, Sir2, SIRT1, -2 and 3 share four proximal cysteines that can indicate the possibility of binding zinc (figure 2). These four Cys are highly conserved among these sirtuins and just following the catalytic histidine. Then, although this Zinc ion must be not involved in the catalytic activity, their presence can be important for the maintenance of the structure of the sirtuin. In fact, recently Sanders and coworkers (Sanders et al., 2010) have shown that the four-cysteine metal binding site resembles the Zn-ribbon structure of transcription factors such as TF-IIS, TF-IIN and RNA polymerase II subunit RPB9. Further, although the Zinc-binding site is too far from catalytic domain, its presence is important for the activity of the enzyme since the change of any cystein to alanine or addition of zinc chelators inhibits the *in vitro* deacetylase activity of sirtuins (Min et al., 2001).
Regarding post-translational regulatory mechanisms, sirtuins can be regulated by phosphorylation and sumoylation. In fact, in SIRT1 thirteen residues have been found to be phosphorylated *in vivo* (Sasaki et al., 2008) indicating a high ratio of regulation by kinases. Further, dephosphorylation by protein phosphatases *in vitro* results in the decrease of the NAD^+-dependent deacetylase activity in SIRT1. On the other hand, sumoylation of SIRT1 at

Lys734 residue has been also reported (Yang et al., 2007). Sumoylation consist in the binding of small ubiquitin-like modifier (SUMO) proteins to lysine residues (Hay, 2001). Binding of SUMO protein to SIRT1 increases its deacetylase activity and mutation of SIRT1 at the Lys734 residue or desumoylation by the nuclear desumoylase SENP1 reduces the activity (Yang et al., 2007).

Finally, another regulatory mechanism also establishes a relationship of sirtuins with metabolism. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is physiologically nitrosylated at its Cys150 residue and binds to Siah1. Further, the complex moves to the nucleus since Siah1 show a nuclear localization signal. In the nucleus, Siah1 interacts with SIRT1 and other proteins. By this mechanism, S-nitrosylation of SIRT1 by GAPDH inhibits its deacetylase activity but specifically in the nucleus (Kornberg et al., 2010).

2.1 Enzymatic activity of sirtuin

As it has been above indicated (figure 1) sirtuins bind a Nε-acetyl-lysine of the target protein and deacetylate it by using NAD^+ as substrate and producing NAM and 2′-O-AADPR (Hirsch & Zheng, 2011). However, this mechanism is no completely clear. In the case of SIRT6, although the deacetylation of histone 3 by SIRT6 has been described (Kawahara et al., 2009), other authors indicate that the main activity of this sirtuin is the ADP-ribosylation (Liszt et al., 2005). However, more recent studies indicate that the ADP-ribosyl-transferase of sirtuins could be only some inefficient side reactions of the deacetylase activity without any relevant physiological role (Du et al., 2009).

2.2 Subcellular localization of sirtuins

One of the key facts that determine the main targets of the different members of the sirtuin family is their respective subcellular localization. SIRT1 is found in the cell in both, the cytosol and the nucleus although it seems that nuclear localization is the most prevalent. However, recent research has demonstrated that SIRT1 is mainly sequestered in cytosol in highly glycolitic tumoral cells (Stunkel et al., 2007) indicating a metabolic-dependent localization of this deacetylase. On the other hand, SIRT3 is predominantly found in mitochondrial matrix (Schwer et al., 2002) although some studies have shown nuclear and also cytosolic locations (Sundaresan et al., 2008) whereas other authors have reported an exclusive mitochondrial localization (Cooper & Spelbrink, 2008). In the case of SIRT2, this sirtuin appears to be exclusively cytoplasmic (North & Verdin, 2007). SIRT4 and SIRT5 are located in the inner mitochondrial membrane or matrix (Michishita et al., 2005) and SIRT6 and SIRT7 are located in the nucleus (Schwer & Verdin, 2008).

2.3 Modulation of sirtuin levels

Acting as metabolic sensors, these proteins respond to many processes that affect the energetic balance in the organism including aging, dietary interventions, fasting or exercise. Aging progress is associated with a gradual decline of several physiological processes in the organism. In heart, age-related in SIRT1, decline is accompanied by a higher level of oxidative stress and the decrease in the expression of endogenous antioxidant enzymes and their regulators (Ferrara et al., 2008). In central nervous system, aging results in decreased activity of SIRT1 in cerebellum that leads to the increase in acetylation of protein residues specially affecting motor function (Marton et al., 2010). In cell culture models, cellular senescence induced by ionizing radiation is accompanied by the decrease in the levels of SIRT1 (Hong et

al., 2010). On the other hand, the contrary effect of aging has been reported. In rats, an age-related increase in SIRT1 levels has been shown in skeletal muscle (Koltai et al., 2010).

Caloric restriction (CR) is the only dietary modification able to extend median and maximum lifespan in a number of organisms from yeast to mammals (Lomb et al., 2010). The effect of CR on lifespan extension is thought to be dependent on multiple different signaling pathways. CR decreases the activity of pro-aging pathways such as oxidative stress and insulin and growth hormone signaling whereas it stimulates the endogenous capacity of the cells against stress including antioxidant mechanisms (Qiu et al., 2010), DNA repair capacity and autophagy (Morselli et al., 2010). Further, the activity of mitochondria is modified in CR. Under CR, mitochondria show higher efficiency with lower reactive oxygen species production (Lopez-Lluch et al., 2006).

Many of the effects of CR on longevity have been associated to the induction of sirtuin activity in cells (Cohen et al., 2004). Studies performed in mice have demonstrated that SIRT1 protein levels increases during CR in many tissues including brain, white adipose tissue, muscle, liver and kidney (Kanfi et al., 2008). Moreover, loss-of-function and gain-of-function mouse studies have provided genetic evidences that indicate that SIRT1 is a key factor in the physiological response to CR (Imai, 2009). It is also important to highlight that SIRT1 has been related to the central response to low nutritional availability at the hypothalamus level probably playing an important role in the regulation of the whole metabolism in mammals (Satoh et al., 2010). Further, SIRT6 levels are also modulated by nutrient availability in a p53-independent mechanism. SIRT6 modulation is mainly through the stabilization of protein levels but not via increase of SIRT6-gene transcription (Kanfi et al., 2008).

The practice of exercise has been also considered to promote longevity and activate common pathways to CR probably by producing a metabolic stress in the organism (Lanza et al., 2008). Then, as in the case of CR, exercise also modulates the levels of sirtuins. In muscle, SIRT1 levels increases along aging and exercise training further increase the relative activity of this sirtuin (Koltai et al., 2010) indicated by an strong inverse correlation between nuclear activity of SIRT1 and the level of acetylated proteins. On the other hand, age-associated increase in SIRT6 levels is attenuated by exercise (Koltai et al., 2010). Exercise also increases SIRT3 expression in muscle and its activity is associated with a higher activity of AMP-dependent protein kinase (AMPK), cAMP-response element binding (CREB) and Peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) indicating its importance in mitochondrial biogenesis in muscle fibers especially in respiratory type I fibers (Palacios et al., 2009).

In heart, the aging-related decrease in MnSOD and catalase expression accompanied by the increase in oxidative damage levels indicated by TBARS and 4-HNE has been related to the decrease in the expression of SIRT1 (Ferrara et al., 2008). Exercise increases SIRT1 levels in heart reverting aging-related effect on MnSOD and catalase levels and its regulatory transcription factor, FOXO3a levels (Ferrara et al., 2008). Exercise not only modulates sirtuin levels in muscle or heart but also can modulate sirtuin levels and activity in central nervous system. Further, the modulation of SIRT1 by natural polyphenolic flavonoids such as resveratrol or quercetin may exert important beneficial effects in exercise performance (Lappalainen, 2011).

Sirtuin expression is also altered in cancer cells (Ashraf et al., 2006). This fact is important because these cells show a distinctive metabolism and higher growth in comparison with non-transformed cells. The different pattern of sirtuin expression in tumoral cells would confer to these cells higher resistance against exogenous agents and also control a different metabolism.

Other important issue in the regulation of sirtuin levels is the complex and new world of microRNAs (miR)-dependent regulation. Currently, the study of the regulation of sirtuin expression by microRNAs has demonstrated that these proteins are also regulated by this system. MiR-34a is markedly reduced in p53-null PC3 cells and its overexpression inhibits SIRT1 expression at the transcriptional level indicating a p53-dependent regulation of SIRT1 levels (Fujita et al., 2008). On the other hand, in mesenchimal transition processes in breast cancer, the downregulation of miR-200 has been related to the increase in the levels of SIRT1 in these cells contributing to the tumoral phenotype (Eades et al., 2011). On the other hand, the release of proinflammatory mediators in adipocytes in serum-free conditions is regulated by the inhibition of SIRT1 expression mediated by miR-132 (Strum et al., 2009). Further, miR-199a also represses SIRT1 in cardiomyocytes and its downregulation in low oxygen tension conditions derepresses SIRT1 expression at the same time than HIF-1α (Rane et al., 2009). Other interesting miRs, miR-33a and b, are involved in the regulation of fatty acid oxidation including the levels of SIRT6. Increase in the levels of miR-33a and b decrease fatty acid oxidation and also insulin signaling in hepatic cell lines indicating a regulatory role of these miRs in important metabolic pathways in the cell (Davalos et al., 2011). Taken together, it is clear that the, to date, poorly clarified regulatory mechanisms depending on miRs complicate the regulatory mechanisms of sirtuin levels at posttranscriptional level.

During last years, small polyphenol molecules have also demonstrated capacity to increase sirtuin activity. Some years ago, we and others demonstrated that resveratrol, a polyphenol of the family of stilbenes found in grapes, dry fruits and berries, is able to extend lifespan in mice fed under high fat conditions (Baur et al., 2006). In this process, sirtuin activity was considered as an important factor. From them, several other works have demonstrated the importance of resveratrol and related compounds in sirtuin-dependent metabolic modifications. In fact, resveratrol is able to modulate insulin response (Zhang, 2006), and also regulate AMPK activity (Dasgupta & Milbrandt, 2007). In some cases, these effects have been related to sirtuin activity and in others, a sirtuin-independent effect has been suggested. In any case, in our hands resveratrol have shown capacity to increase SIRT1 and SIRT3 levels in cultured cells indicating the capacity to modulate sirtuin expression (Santa-Cruz Calvo et al., unpublished results), accordingly with already published results (Costa Cdos et al., 2011; Kao et al., 2010; Sulaiman et al., 2010).

3. Sirtuin-dependent metabolic regulation

As its can be concluded by the complexity of sirtuin interactions, the different partners and regulatory processes, this family of deacetylases is involved in many different physiological mechanisms in cells. In the following sections we are going to resume the most important findings about the role of these enzymes in metabolic control in relationship with the aging process. Taken into consideration that metabolic processes are involved in all the cellular processes, metabolic control by sirtuins is the most important function of these enzymes (Yu & Auwerx, 2009).

3.1 SIRT1

Looking inside this deacetylase enzymes family, SIRT1 is one of the members that show more interactions and that respond to more factors. Mammalian SIRT1 has multiple targets including histones, transcription factors and other molecules that collectively modulate

several processes such as energy metabolism, stress response and cell survival (Tang, 2011). Its activity may decline with aging in many tissues and it has been proposed that its reactivation can produce beneficial effects (Tang, 2011).

One of the most important factors involved in the metabolic control regulated by SIRT1 is PGC1α. SIRT1 functionally interacts with PGC1α and deacetylates it (Nemoto et al., 2005). Deacetylation of PGC1α activates this transcription factor that induce the expression of nuclear respiratory factor 1 (NRF1) and then, mitochondrial biogenesis. In fact, activation of SIRT1 induces deacetylation of PGC1α and FOXO1 that finally control the transcriptional modulation for lipid catabolism (Canto et al., 2010). Further, deletion of SIRT1 alters fatty acid metabolism resulting in hepatic steatosis and inflammation (Purushotham et al., 2009). SIRT1-dependent regulatory mechanisms regulate the switch from carbohydrate to lipid as main energy sources in muscle. Limitation in glucose availability during fasting or exercise induces AMPK activity in muscle that acts as a prime initial sensor that activates SIRT1. PGC1α is acetylated by the acetyltransferase GCN5 that together with SIRT1 control its regulation depending on nutritional status (Dominy et al., 2010). Activity of this GCN5 or inhibition by nicotinamide reduces SIRT1-dependent PGC1α acetylation and decreases the expression of genes involved in mitochondrial biogenesis in muscle (Gerhart-Hines et al., 2007). Further, PGC1β is also acetylated on at least 10 lysine residues by GCN5 repressing its transcriptional activity, SIRT1 activity also deacetylates it and restores transcriptional activity (Kelly et al., 2009).

As a cycle of regulation, SIRT1 also controls the expression levels of PGC1α in skeletal muscle through stimulation of its promoter activity probably with the activity of myogenic factors such as MEF2 and MyoD (Amat et al., 2009). On the other hand, PGC1α is also involved in sirtuin expression since, as mitochondrial biogenesis is activated and some sirtuins are located in mitochondria, the expression of SIRT3 gene is also controlled by PGC1α. This regulation is key in the differentiation of brown adipocytes (Giralt et al., 2011).

Besides the high number of evidences demonstrating the relationship of SIRT1 activity and PGC1α-dependent mitochondrial biogenesis, some other works indicate that SIRT1 overexpression reduces mitochondrial biogenesis (Gurd et al., 2009). This last paper is based on the correlation of SIRT1 levels with mitochondrial biogenesis. In this context, a recent paper indicate that there are a direct relationship between mitochondrial biogenesis and activity of PGC1α with nuclear activity of SIRT1 although not with its protein content in skeletal muscle cells (Gurd et al., 2011) indicating that sirtuins levels are not necessarily related to the activity of these enzymes.

Another of the most studied targets of SIRT1 is the tumor suppressor p53. SIRT1 deacetylates K382 of p53/TP53 and inhibits its transcriptional activity impairing then, its ability to induce proapoptotic mechanisms and to modulate cell senescence. Further, it has been also reported that H_2O_2-induced cell senescence is accompanied by accumulation of acetylated p53 by decrease in the function of SIRT1 (Furukawa et al., 2007). Taken into consideration the role of p53 in nuclear and mitochondrial apoptosis (Moll & Zaika, 2001), SIRT1 seems to be a p53-dependent antiapoptotic factor.

On the other hand, modulation of p53 by SIRT1 also produces effects on cell metabolism since p53 seems to regulate mitochondrial respiration and glycolysis (Ma et al., 2007). In fact, p53 regulates the transcription of cytochrome c oxidase 2, an important factor in assembly of the cytochrome c oxidase complex (Fields et al., 2007), and then, an important factor in mitochondrial respiration. Then, high levels of SIRT1 in tumor cells will block p53-

dependent SCO2 transcription and contribute to the Warburg effect found in these cells. However, the relationship between SIRT1 and p53 is more complex at the transcriptional level. Transcription of SIRT1 is repressed by p53 via p53 response elements in its proximal promoter (Naqvi et al., 2010). However, another p53 binding site has been reported in the distal promoter of SIRT1. This binding site is necessary for SIRT1 induction under caloric restriction (Naqvi et al., 2010). In this site, p53 competes with the Hypermethylated-In-Cancer-1 (HIC1) transcriptional repressor and, then, activation of p53 derepresses SIRT1 transcription. Taken together all the information available about p53 and SIRT1 interaction, more research is be necessary to clarify the complex system p53-SIRT1 and regulation of mitochondrial activity.

All these regulations implicate a contradictory role of SIRT1 in modulation of mitochondrial biogenesis and respiratory metabolism. If SIRT1 is activating PGC1α by deacetylation and, then, inducing mitochondrial biogenesis, downregulation of the activity of p53 by the same SIRT1 will reduce the respiratory capacity by affecting SCO2 levels and Complex IV assembly. This contradictory effect would be explained by the different location of SIRT1 and then, modulation of different regulatory processes. Further, some other studies have indicate that despite the role of SIRT1 as deacetylase of p53, SIRT1 has little effect on p53-dependent transcription and does not affect many of the p53-mediated biological activities (Kamel et al., 2006). If these results are confirmed, they would explain how mitochondrial biogenesis and p53-repression can occur at the same time. Future research will clarify this complex regulation of mitochondrial respiratory metabolism.

3.2 SIRT2

The human SIRT2 is predominantly a cytosolic protein known to be a tubulin deacetylase (North et al., 2003). SIRT2 deacetylates lysine-40 of α-tubulin and then, its knockdown results in tubulin hyperacetylation. Levels of SIRT2 increases dramatically during mitosis and is also phosphorylated during the G_2/M transition. Then, SIRT2 is an important factor in the control of mitotic exit in the cell cycle (Dryden et al., 2003). Further, its interaction with the homeobox transcription factor, HOXA10, raises the possibility that SIRT2 also plays a role in mammalian development (Bae et al., 2004). The importance of tubulin activity in neuronal activity probably explains the important role ascribed to SIRT2 in neurodegenerative diseases (Harting & Knoll, 2010).

Regarding metabolism, information about SIRT2 is very limited and seems to indicate a lipid inhibitory role of this sirtuin in contrast with the role found with SIRT1 and 3. Its presence has been inversely correlated with the differentiation of preadipocytes to adipocytes by modulating the activity of FOXO1 (Jing et al., 2007). SIRT2 deacetylates FOXO1 and enhances its repressive interaction with PPAR-γ, an essential factor in adipocyte differentiation (Wang & Tong, 2009). In contrast with the neuroprotection reported in some neurodegenerative processes, a neuroprotective effect of the decrease of sterol biosynthesis through SIRT2 inhibition has been also shown in the case of Huntington's disease (Luthi-Carter et al., 2010). On the other hand, silencing of SIRT2 induces intracellular ATP drop and cell death in neuronal PC12 cells (Nie et al., 2011) indicating metabolic regulatory mechanisms of this sirtuin. Further, the role of SIRT2 in expression of antioxidant systems has been also reported. Induction of MnSOD seems to depend on deacetylation of FOXOa by SIRT2 (F. Wang et al., 2007).

3.3 SIRT3

One of the most important sirtuin in metabolic regulation is SIRT3. Its localization into mitochondria and the diversity of targets including both metabolic and antioxidant components makes it in one of the immediate regulators of mitochondrial activity. In a recent paper, Kendrick and co-authors found that mice fed under high-fat diet develop fatty liver and show high levels of acetylated proteins in parallel with a decrease in SIRT3 activity (Kendrick et al., 2011). Moreover, deletion of SIRT3 further increases acetylation in high-fat fed animals and reduces the activity of respiratory complexes III and IV indicating a key role of this sirtuin in mitochondrial activity control. One of the direct targets of SIRT3 is succinate dehydrogenase (SDH, Complex II). Acetylated SDH show low activity and deacetylation by SIRT3 activates it (Finley et al., 2011). These papers indicate the important role of SIRT3 in the regulation of mitochondrial activities by deacetylation.

The role of SIRT3 in acetate metabolism has been also related to aging (Shimazu et al., 2010). Acetate plays an important role in cell metabolism being an important product of ethanol and fatty acid metabolism especially during fasting or starvation (Seufert et al., 1974). Acetate can be converted into acetyl-CoA by the activity of acetyl-CoA synthase enzymes in cytosol (AceCS1) or mitochondria (AceCS2). These enzymes are activated by deacetylation by both SIRT1 in cytosol and SIRT3 in mitochondria (Shimazu et al., 2010). An important role for SIRT3 in acetate metabolism has been suggested since both, SIRT3 KO and AceCS2 KO mice show overlapping phenotypes. However, to date no clear data about the role of acetate in aging process have been shown although AceCS-mediated synthesis in yeast has been associated with higher longevity (Falcon et al.).

The importance of SIRT3 in the protection against oxidative stress is also important since the protective effect of CR on oxidative stress is diminished in mice lacking SIRT3. This sirtuin is involved in the reduction of cellular ROS levels depending on the manganese-dependent mitochondrial superoxide dismutase 2 (MnSOD or SOD2) (Qiu et al., 2010). SIRT3 adjusts MnSOD activity to the mitochondrial nutrients availability and then, the production of mitochondrial ROS (Ozden et al., 2011). In this regulation, SIRT3 deacetylates two important lysine residues on SOD2 promoting its antioxidant activity.

Levels of SIRT3 are also regulated by the energetic status of the organism. SIRT3 levels increase by caloric restriction of exposure to low temperatures in brown adipocytes. Forced expression of SIRT3 and activity in a cell line for brown adipocytes enhances the expression of PGC1α, UCP1 and another mitochondria-related genes whereas mutation of SIRT3 inhibits PGC1α-dependent UCP1 expression (Shi et al., 2005). Diet and exercise signals also regulate SIRT3 and activate the AMPK and PGC1α in skeletal muscle cells (Palacios et al., 2009) whereas this activation is much lower in SIRT3 KO animals. On the other hand, PGC1α strongly stimulates mouse SIRT3 gene expression in muscle cells and hepatocytes (Kong et al., 2010) through binding to an oestrogen-related receptor binding element (ERRE) in its promoter region. Induction of SIRT3 is also essential for mitochondrial biogenesis and the expression of several of mitochondrial components including antioxidant systems (Kong et al., 2010).

Taken together, SIRT3 seems to be a key sirtuin that senses metabolic status through NAD^+/NADH levels at the mitochondria and then, integrates respiratory metabolism and antioxidant systems.

3.4 SIRT4 and SIRT5

SIRT4 and SIRT5 are also mitochondrial sirtuins involved in the regulation of other metabolic processes essentially related with the urea cycle (Li & Kazgan, 2011). One of the main activities of SIRT4 in mitochondria is the downregulation of insulin secretion by beta cells by repressing the activity of glutamate dehydrogenase in response to aminoacids (Argmann & Auwerx, 2006; Haigis et al., 2006). Depletion of SIRT4 have also shown that this sirtuin seems to exert an opposite role than SIRT1 and SIRT3 since its depletion increases gene expression of fatty acid metabolism enzymes in hepatocytes (Nasrin et al., 2010). However, this effect is indirect due to compensatory mechanisms involving higher expression of SIRT1. However, putative contrary effects of this sirtuin in relationship with other members of the family cannot be discarded and further research involving specific inhibitors instead of gene depletion is needed.

In the case of SIRT5, this sirtuin, mainly located at the matrix of the mitochondria, is also involved in the regulation of the urea cycle (Nakagawa & Guarente, 2009). SIRT5 deacetylates the mitochondrial carbamoyl phosphate synthetase 1. This enzyme is the first and rate-limiting step of the urea cycle (Nakagawa & Guarente, 2009). Furthermore, deacetylation of cytochrome c has been also reported although the effect of this deacetylation in both, respiration or apoptosis, is not clear (Schlicker et al., 2008). To date, no other substrates of SIRT5 have been reported.

3.5 SIRT6 and SIRT7

SIRT6 is predominantly a nuclear protein broadly expressed in tissues showing the highest levels in muscle, brain and heart (Liszt et al., 2005). In any case, SIRT6 is mainly involved in DNA damage repair and is located in the nucleus. It is recruited to the sites of DNA double-strand breaks (DSBs) and stimulates DSB repair through both, nonhomologous end joining and homologous recombination by stimulating PARP-1 poly-ADP-rybosilase activity (Mao et al., 2011).

It seems that this sirtuins is closely involved in neural degeneration related to aging. In fact, a mice model lacking SIRT6 develops a degenerative disorder that mimics models of accelerated aging (Lombard et al., 2008, Mostoslavsky et al., 2006). This effect depends on a higher instability through the DNA base excision repair pathway, then, the accumulation of mutations in the genome leads to aging-associated degenerative phenotypes (Mostoslavsky et al., 2006). Furthermore, SIRT6-deficient mice show deficiency in growth and show severe metabolic defects indicating that the higher DNA-damage found in these animals is linked to a systemic metabolic deregulation that leads to age-related processes and death.

Neural SIRT6 has been also recently related to metabolic homeostasis in mammals. Neural-specific deletion of SIRT6 in mice produces postnatal growth retardation since these animals show low growth hormone (GH) and also insulin-like growth factor 1 (IGF1) levels (Schwer et al., 2010). However, unlike SIRT6-KO animals that die by hypoglycaemia and other severe metabolic defects (Mostoslavsky et al., 2006), neural-SIRT6 KO animals, reach normal size and even become obese. It seems that at the central nervous system, SIRT6 acts as a central regulator of somatic growth and metabolism by modulating neuroendocrine system. It seems that the main mechanism of action of SIRT6 in the regulation of gene expression and the control or systemic metabolism and aging is through the deacetylation of lysine 9 in histone H3. Recently it has been shown that hyperacetylation of H3K9 found in SIRT6-deficient cells leads to a higher NF-κB-dependent modulation of gene expression,

proinflammatory processes, apoptosis and cellular senescence (Kawahara et al., 2009). Then, the control of gene expression by histone modulation seems to be a key factor in SIRT6-dependent prolongevity effect.

Furthermore, the activity of SIRT6 in liver has been also reported. Rosiglitazone (RGZ) is used to protect liver against steatosis. This compound increases the levels of SIRT6 in liver at the same time that ameliorates hepatic liver accumulation affecting PGC1α and FOXO1 (Yang et al., 2011). However, in SIRT6-deficient mice, RGZ was unable to decrease fat accumulation in hepatocytes and to affect PGC1α and FOXO1 activity indicating an important role of this sirtuin in fat storage in liver. In this mechanism, SIRT1 could be also involved since it forms a complex with FOXO3 and NRF1 and activates the expression of SIRT6 (Kim et al., 2010). In this case SIRT6 would be the sirtuin that negatively regulates glycolysis, triglyceride synthesis and fat metabolism by deacetylating H3K9 and then, modifying the activity of the promoters of many genes involved in metabolic processes. In fact, the specific deletion of SIRT6 in liver causes profound alterations in gene expression that produce the contrary effects in glycolysis, triglyceride synthesis and fat metabolism.

The last member of sirtuins, SIRT7, is widely expressed in nucleolus and has been associated with active rRNA genes interacting with RNA polymerase I and with histones (Ford et al., 2006). This sirtuin is controlled by CDK1-cyclin B-dependent phosphorylation and dephosphorylation indicating that its activity is required to resume rDNA transcription in late telophase (Grob et al., 2009). In the case of SIRT7, studies performed by using murine cells lacking or overexpressing this sirtuin demonstrate that it is related with the tumorigenic potential and may enable cells to sustain critical metabolic functions because it inhibits cell growth under severe stress conditions (Vakhrusheva, Braeuer et al., 2008). These studies have also demonstrated the important role of this sirtuin in lifespan. In fact, mice lacking SIRT7 undergo reduction in mean and maximum lifespans and develop heart hypertrophy and inflammatory cardiopathy (Vakhrusheva, Smolka et al., 2008) probably by the impossibility to deacetylate p53 and regulate p53-dependent apoptosis.

4. Sirtuins: Antioxidant mechanisms and autophagy

Other of the important roles of sirtuins related to metabolism and aging is based on their activity to maintain cellular antioxidant mechanisms and autophagy systems. A great body of evidence has accumulated indicating that at the same time that sirtuins are modulating metabolism, they also regulate, in a coordinated mechanism, antioxidant systems and recycling systems in cells.

Altered ROS levels are observed in several age-related illnesses including carcinogenesis, neurodegenerative, fatty liver, insulin resistance, cardiac resistance, etc. In mitochondria MnSOD is the primary ROS scavenging enzyme to converts superoxide to hydrogen peroxide that is further converted to water by catalase and other peroxidases. In this mechanism SIRT3 exert a key role since changes in lysine acetylation modifies MnSOD activity in mitochondria (Ozden et al., 2011). Further, CR effect depends, at least in part, on sirtuin regulation but at the same time oxidative stress is reduced in CR by activation of antioxidant systems such as SOD2 in mitochondria by SIRT3 (Qiu et al., 2010).

In heart, the aging-related decrease in MnSOD and catalase expression accompanied by increase in the levels of oxidative damage indicated by TBARS and 4-HNE has been related to the decrease in the expression of SIRT1 (Ferrara et al., 2008).

Regarding recycling mechanism a correct balance between biogenesis and recycling of damaged structures is essential to maintain a correct homeostasis in the cell. Caloric restriction induces autophagy through induction of SIRT1. Transgenic expression of SIRT1 in human cells and in *C. elegans* induces autophagy whereas knockout of SIRT1 in the same cells and organisms prevents autophagy induced by resveratrol or nutrient deprivation (Morselli et al., 2010). Autophagy induction has been also related to the extension of lifespan by some agents such as spermidine and resveratrol in organism such as yeast, nematodes and flies (Morselli et al., 2009). In this process, deacetylation of FOXO3 by SIRT1 seems to be essential to the induction of the expression of genes involved in autophagy in caloric restriction (Kume et al., 2010). FOXO is an essential factor in the induction of autophagy and, as it has been above commented, in the antitumoral role of sirtuins (Zhao et al., 2010).
All these works and some other more indicate that sirtuins not only control metabolism regulating essentially mitochondrial respiration and fatty acid oxidation but also regulate in a coordinated way the expression and activity of endogenous antioxidant systems and autophagy processes to eliminate damaged structures including mitochondria.

5. Sirtuins, prolongevity or healthspan effect?

The prolongevity effect of sirtuins was initially determined in yeast (Kaeberlein et al., 1999) and lower metazoan such as *C. elegans* (Tissenbaum & Guarente, 2001) and in *D. melanogaster* (Rogina & Helfand, 2004). However, very recently, these results have been revised and the prolongevity effect of sir2 in these animals has been related to transgene-linked genetic effects other than overexpression or sir2.1 in *C. elegans* or dSir2 in *D. melanogaster* (Burnett et al., 2011; Viswanathan & Guarente, 2011). Further, along last year, a considerable body of evidences indicates the controversial aspect of sirtuins in longevity studies. Calorie restriction clearly exerts a prolongevity effect on many organisms. In this effect, sirtuins were described as important factors in yeasts (Lin et al., 2000), *C. elegans* (Y. Wang & Tissenbaum, 2006) and *D. melanogaster* (Rogina & Helfand, 2004). However, other studies in yeast and *C. elegans* have argued about the role of sirtuins in caloric restriction-dependent longevity (Kaeberlein, 2010; Kenyon, 2010). Further, in mammals, overexpression of SIRT1 in mice does not increase lifespan (Herranz & Serrano, 2010).
These new concerns about the promising role of sirtuins in longevity do not affect other important functions of sirtuins in cell physiology. There is also an overwhelming body of evidences indicating that sirtuins play a crucial role in metabolic homeostasis. As, the activity of sirtuins depends strictly on the levels of NAD^+ which acts as co-substrate in the deacetylation activity catalyzed by sirtuins, changes in NAD^+ levels, reflecting modifications in the metabolic status of the cells, would modulate sirtuin activity. NAD^+-dependence for sirtuin activity in cells confers to sirtuins the integrative role of metabolic sensors that modulates cell changes depending on the metabolic status of the cells. Furthermore, the broad group of targets of sirtuins activity in cells confers to these proteins the capacity to modulate executive proteins and also to influence transcription factors and histone proteins to change not only protein activity but also gene expression profile in cells accordingly to changes in metabolism (Canto & Auwerx, 2009).
In mammals, SIRT1 mediates the metabolic and transcriptional adaptations after nutrient deprivation or energy stress changes. These adaptations are centered in a higher respiratory activity of mitochondria. Calorie restriction induces the expression of sirtuins in many tissues and likely this regulation is related to the changes in metabolism found under

dietary restrictions (Bamps et al., 2009; Imai, 2009). Overexpression of SIRT1 in mice protects animals against metabolic damage caused by a fat-rich diet (Herranz et al., 2010). On the other hand, mice lacking SIRT1 show deficiencies in metabolism and are unable to increase lifespan in calorie restriction conditions (Herranz & Serrano, 2010). Further, resveratrol, a polyphenol considered as activator of sirtuins protects against metabolic and age-related diseases (Lagouge et al., 2006) and also increase lifespan in animals fed with fat-rich diets (Baur et al., 2006). However, accordingly with the above indicated recent studies that indicate that sirtuins do not affect longevity, in normal diet conditions, resveratrol is unable to increase lifespan in mice although delays age-related deterioration (Pearson et al., 2008). Many researchers have also demonstrated the role of sirtuins in protection of cell and tissues against different forms of injury through activation of FoxO and intracellular antioxidant systems (Hsu et al., 2010).

It has been recently proposed that energy metabolism can be importantly involved in the accumulation of high levels of advanced-glycosylation end (AGES)-products into cells and, then, in the impairment of cell and tissue activity (Hipkiss, 2008). In this process, NAD^+/NADH ratio is importantly involved. Decrease of NAD^+ availability in ad libitum conditions decreases metabolism of triose phosphate glycolytic intermediates such as glyceraldehydes-3-phosphate and dihydroxyacetone-phosphate. These compounds can spontaneously decompose into methylglyoxal (MG), a highly toxic glycating aging that produces AGES. AGES and MG can be involved in mitochondrial dysfunction, the increase in ROS production and also affect gene expression and intracellular signaling. However, under CR or exercise NADH is oxidized to NAD^+ and also NAD^+ synthesis is activated. NAD^+ not only activate sirtuins but also reduces the levels of MG and then, reduces the deleterious effects of this compound (Hipkiss, 2008). This hypothesis directly links metabolism and its regulation to cell damage and then to aging indicating that sirtuins are directly involved in a more balanced metabolism and then, are important factors to be considered in aging, longevity and healthspan. Taken together, it seems clear that sirtuins are key factors in metabolic homeostasis and can increase healthspan and also show prolongevity effects in conditions of metabolic stress such as western food rich in unsaturated fat.

6. Conclusion

In the present chapter we have resumed the complex system regulated by sirtuins and involved in metabolic aspects that affect aging. Aging is a process that courses with the accumulation of damage into cells and organs. Most of the energy spent by cells is used to maintain the biological structures and the order into cells and tissues. When energy is deficient or the injury increases, damage in cells accumulates in structures that cannot be eliminated and that disturb their correct physiologic mechanisms. Accumulation of aberrant structures ends in the incapacity of cells to function properly and then, produce the decline in functionality found in aging. Sirtuins are key factors in this process. These deacetylases link energetic status of the cell with regulation of aerobic metabolism, reparation activities and antioxidant systems preventing the accumulation of damaged structures. Although the right role of these sirtuins in longevity is currently questioned, their activity as core of several regulatory processes make them important regulators in, at least, the correct physiology of the organism until death.

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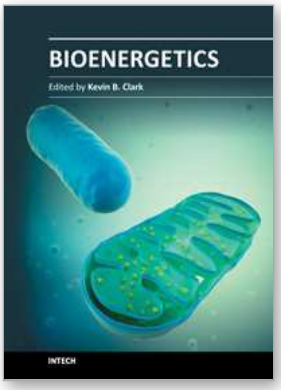

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Cellular life depends upon energy storage, transformation, utilization, and exchange in order to optimally function and to stay-off death. The over 200-year-old study of how cells transform biological fuels into usable energy, a process broadly known as bioenergetics, has produced celebrated traditions in explaining origins of life, metabolism, ecological adaptation, homeostasis, biosynthesis, aging, disease, and numerous other life processes. InTech's edited volume, Bioenergetics, brings together some of these traditions for readers through a collection of chapters written by international authorities. Novice and expert will find this book bridges scientific revolutions in organismic biology, membrane physiology, and molecular biology to advance the discipline of bioenergetics toward solving contemporary and future problems in metabolic diseases, life transitions and longevity, and performance optimization.

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