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The Relationship between the Sirtuins and Slowing the Aging

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Abstract

Originally rising to notoriety for their function in regulating the aging, sirtuins are a group of NAD-dependent enzymes that are related to a steadily increasing some biological processes. In addition to controlling aging, sirtuins play key roles in maintaining the organism metabolic homeostasis. These enzymes have primarily preventative roles in the development of many age-related diseases, including cancer, neurodegeneration, and cardiovascular diseases. Seven isoforms of this enzyme have been specified in mammals, (SIRT1–7), all of them involve a conserved catalytic core and show differential subcellular localization and activities. Oxidative stress can affect the activity of sirtuins at different levels: expression, post-translational modifications, protein-protein interactions, and NAD levels. Mild oxidative stress induces the expression of sirtuins as a compensatory mechanism, while harsh or prolonged oxidant conditions result in dysfunctional modified sirtuins more prone to degradation by the proteases. Oxidative post-translational modifications have been identified in vitro and in vivo, in particular, cysteine oxidation and tyrosine nitration. Nevertheless, further studies are necessary to find out the molecular mechanisms of redox regulation of sirtuins to further design appropriate pharmacological interventions.

Keywords: Sirtuins, Maintenance, Oxidative, Nicotinamide group, NAD biosynthesis.

Introduction

Aging

Sirtuins can regulate of the life span in simple organisms, including leaven, worms, and fruit flies (Haigis and Guarantee, 2006). Various research has demonstrated that SIRT1 adjusts the metabolism through the calorie restriction (CR) (Cantó and Auwerx, 2009), a dieting involvement the strongly provides life extension towards considerable type. Moreover, the overexpression of SIRT1 in rats does not influence life extension (Herranz et al., 2010) but it probably, enhances healthy aging by keeping the body safe against various age-related disorders (Guarantee, 2011).

The strong relation between sirtuins and preventing aging influences of CR brought from SIRT3, which go between the prohibitions of age-concerning meeting damage by CR. Moreover, damage to hearing is an aging characteristic due to damage in the spiral ganglion in the cochlea of the inner ear (Liu and Yan, 2007). Uncommonly, CR increases the hearing damage and is harmful in rats, while Sirt3-weak rats are sensitive to the complications of CR. Moreover, SIRT3 is needed for lowering the CR-mediated damages in various tissues through the glutathione antioxidant function. In addition, SIRT3 has been observed to immediately reduce the cellular reactive oxygen species (ROS) by damage superoxide dismutase (Tao et al., 2010). This provides a wide function for SIRT3 in adjusting age-related pathologies that rely on cellular levels of ROS.

More studies about the effect of sirtuins on a long-life showed that the overexpression of SIRT6 increases life span in rats (Kanfi et al., 2012). Besides, Sirt6 knock-out in mice resulted in aging (Mostoslavsky et al., 2006), which demonstrated that mammalian sirtuin, has an important role in life extension. Especially Lombard and Miller (2012) showed that the life span extension appears to be unassuming and males-specific for causes that stay unclear. Regardless of the decreased standard of insulin-like growth factor 1 (IGF-1) in plasma, observable characteristics before supported with life extension planning, “anti-aging” influence of SIRT6 demonstrated by SIRT6 effective as a tumor inhibition.

Sirtuins Structure

Crystal structure of sirtuins from archaea to eukaryotes showed a central catalytic domain containing 245 residues, with Rossmann fold typical for NAD-dependent proteins as well as a Zn2+ binding site, detached by a cleft where the peptide substrate connects (Figure 1). The NAD molecule assumes a prolonged modification binding to a grove among the two areas with the adenine foundation facing the greatest field and the nicotinamide group close to the little field as in figure (1). SIRT1 is the greatest isoform with prolonged N- and C-terminals, that is very elastic, and unconstructed, with sug additional modified active sites. The Zn^{2+} binding site has three antiparallel beta-strands containing two Cys-X-X-Cys preserved motifs separated by 15–20 residues, where a single zinc ion attaches it and has a significant structural

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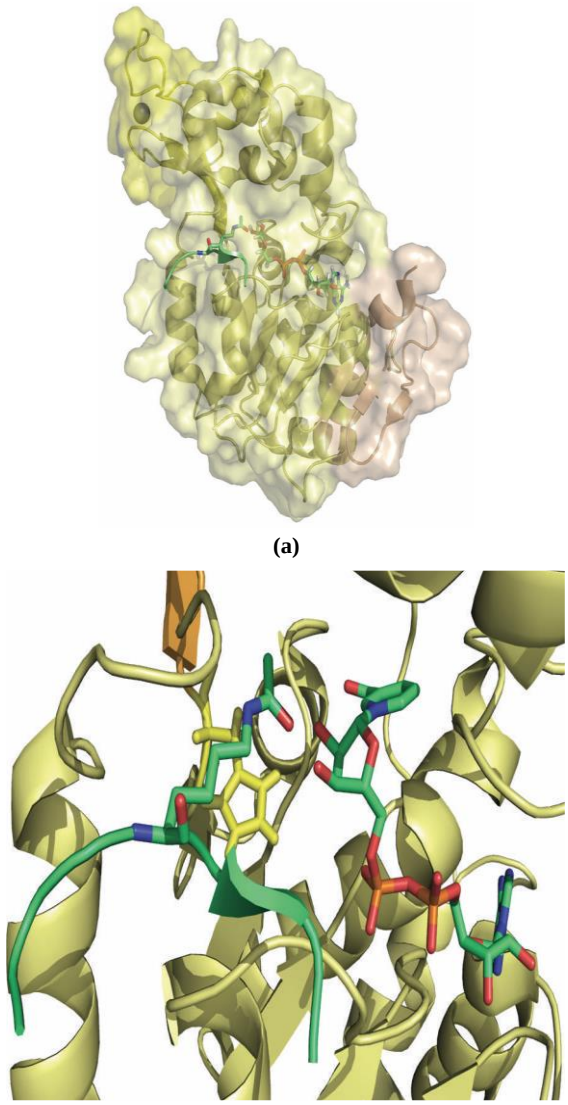
function. It has long been known that replacing these cysteine residues by alanine leads to the protein dysfunction (Sherman et al., 1999). Moreover, it has been shown that zinc tetrathiolate increases the concentrations of zinc and leads to damage to the molecule and its dysfunction (Min et al., 2001).

Another study on P. falciparum showed adding a powerful zinc chelator along with exogenous zinc chloride leads to recovery of both activity and structure the ineffectual Sir2 apoenzyme (Chakrabarty and Balaram, 2010). The zinc ion binds to the small domain, distant from the NAD-binding site, excepting the thing that may happen of involvement in the catalysis, in dissimilarity with other HDAC kinds where zinc is part of the catalytic technique (Finnin et al., 2001).



(a)

(b)

Figure 1: Structure of sirtuins. (a) Crystal structure of a partial sequence of hSIRT1 (PDB 4KXQ) with bound substrates, acetylated peptide, and NAD. (b) Zoom of the catalytic site with the catalytic histidine colored in yellow.

Sirtuin family

The mammalian sirtuins are important protein family with a discrete pattern of subcellular localization. SIRT1 is considered to be mainly localized in the nucleus but also exists in the cytosol. SIRT2 is cytosolic but is also presents in the nucleus. SIRT3, SIRT4, and SIRT5 have been proved to be mitochondrial. SIRT6 is nuclear, and SIRT7 probably is located in the nucleolus (Houtkooper et al., 2012). Almost sirtuins offer protein deacetylase action, like that they deacetylate situated on the inside lysine remains that are acetylated onto their ε-amino groups. Unlike other sirtuins, SIRT4 does not have deacetylase activity but ADP-ribosyltransferase activity (Haigis, et al. 2006), and STAT5 has only a weak deacetylase activity (Du, 2011).

In the issue of acetylation, this capability to be moving backward post-translational amendment rapidly influences a protein's effective and adjusts operations as various as metabolic flow and DNA reform (Wellen and Thompson, 2012). The specific activity of sirtuins, subsequently, could lead to a total deacetylated protein in the cell. Moreover, dieting stress, like fasting or CR, could lead to protein deacetylation (Yang, 2011) A considerable portion of food-encourage deacetylation was observed that happen during the promoted effective of confirmed sirtuins (Hirschey, 2010), the proposition that stress impedance passage stimulated by CR might be controlled, at smaller in portion, on sirtuin deacetylase effectiveness.

Among the mammalian sirtuins, SIRT1 the greatest range comprehensively described for function in the elderly. If we can maintain or enhance SIRT1 activity in the body, we will be able to prevent chronic diseases and lead to a long life span. In a study. the overexpression of SIRT1 in transgenic rats led to a significant lifetime extension compared to the control samples (Herranz, 2010). Moreover, some recent studies suggested that SIRT6 probably is the life-extension factor. Rats with low amounts of SIRT6 display serious metabolic disorders and have a shorter life span (Mostoslavsky et al., 2006). In a study, the overexpression of SIRT6 in male mice led to the life extension in them (Kanfi, 2012). Furthermore, SIRT3 is also suggested to be the sirtuin, related to the human elderly. Several researchers have manipulated the SIRT3 gene to prevent aging.

Enzymatic activity of sirtuins and biosynthesis of NAD

Sirtuins are members of the class III protein deacetylases or histone deacetylases (HDACs) that need to NAD for their enzymatic activities (Imai et al., 2000). NAD is a significant electron carrier agent, which is included in various enzymatic responses (Houtkooper et al., 2010). Due to the distinguishing role of NAD in the enzymatic responses, the efficiency of sirtuins strongly depends on the metabolism of a living organism in the cells. At first, yeast SIR2 was found as a histone deacetylase, but mammalian sirtuins had been also different non-histone protein substrates (Tanner et al., 2000).

Even though most of the sirtuins have deacetylase activity, SIRT4 has been shown to have ADP-ribosyltransferase activity, while

both SIRT1 and SIRT6 have deacetylation and a comparatively weak ADP-ribosyltransferase activity (Michishita et al., 2008). Nicotinamide mononucleotide (NMN) is an endogenous inhibitor of sirtuins and is generally changed to NAD by nicotinamide mononucleotide adenylyltransferase (NMNAT) (Houtkooper et al., 2010).

More recent research showed that the NAD biosynthesis adjusts the effectiveness of sirtuins. Illustrating a general rule, NAMPT-mediated NAD biosynthesis dominances SIRT1 effectiveness in more tissues; and SIRT3, 4, and 5 are adjusted by NAD biosynthesis in reacting to food stress (Nakagawa et al., 2009). Whilst, NAD biosynthesis is related to the circadian clock, brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1), and SIRT1, and in transformation, adjusts SIRT1 activity during the presence of NAD (Ramsey et al., 2009).

Activators of the sirtuin pathways

The deacetylases like sirtuins (SIRT1 to 7) increase life span by various mechanisms and possibility goes between much of advantageous influences of DR (Satoh et al., 2013). Given their beneficial effects in promoting longevity, sirtuins are a very interesting drug target. Sirtuin-activating compounds (STACs) including plant-derived metabolites like natural antioxidant and anthocyanidins immediately activate SIRT1 in vitro through an allosteric technicality, which decreases the substrate Km (Howitz et al., 2003). Resveratrol (3,5,40-trihydroxystilbene) is the first and most potent sirtuin activator and extend life span in various organisms. The detection of natural STACs led to the production of artificial SIRT1 activators that often are powerful, soluble, and bioavailable. More research demonstrated that resveratrol and artificial STACs induce gene expression alterations that are comparable with DR (Hubbard and Sinclair, 2014).

A way of increasing the activity of sirtuins is increasing the NAD delivery to them, which is the most important element they need. Their activity may increase more by increasing the amount of NAD precursors (NMN or NR), through stimulating NAD bioartificial enzymes or preventing the NAD hydrolase (Sinclair et al., 2014). In rats, resveratrol expands lifespan when animals receive great-lipids in their nutrition (Pearson et al., 2008) and also in integration with criterion chow when nutrition per daily (Ja and Ha, 2006), but not when supplied daily with criterion chow (Strong et al., 2013). Among the SIRT1-activating compounds (STACs), which are artificial activators of sirtuins, SRT1720 and SRT2104 are more useful for the life extension of rats' with either a high-calorie or low-calorie nutrition and both keep the rats safe against age-concerning alterations in various tissues involved muscle disadvantage (Minor et al., 2011). Moreover, STACs have been observed to have a significant role in age-related diseases like cancer, diabetes, cardiovascular disease, and liver steatosis (Hubbard and Sinclair, 2014).

More investigations are ongoing to utilize STACs in treating inflammations and autoimmune disorders (Hubbard and Sinclair, 2014). In a study, SRT1720 had a useful effect on the experimentally induced chronic obstructive disease and asthma in rats. Furthermore, it has been useful in neurodegeneration (Zhao et al., 2013), experimental experimentally induced Alzheimer's disease, and multiple sclerosis in rats (Gräff et al., 2013). It inhibits and modifies the overweight and age-related metabolic declines. In rats fed basal diet fortified with a high-calorie, resveratrol and STACs protected the rats against overweight, making the body more sensitive to insulin, increasing the mitochondrial activities, and inhibiting hepatic steatosis (Baur and Sinclair, 2006). Their influences were also observed in nonhuman primates fed a diet with high fat and sugar (Fiori et al., 2013). Results from the research carried out on overweight and elderly rat samples demonstrated that the greater NAD levels protected rats from metabolic disorders and aging (Escande et al., 2012), inflammation, and muscle weakness (Sinclair et al., 2014).

A significance of the results is to use STACs as therapeutic agents for humans (Hubbard and Sinclair, 2014). Resveratrol is also effective with its insulin-sensitive influences (Ghanim et al., 2011) and DR-such phenotypes have been caused to be visible that in aging and overweight humans (Timmers et al., 2011).

In conclusion, sirtuins and their stimulators have significant roles in life expansion, as well as in the prohibition and therapy of a wide range of diseases in rodent models. However, there is not an overall agreement on delay in aging, given wide disagreements with this issue (Ledford, 2010).

Calorie restriction

Calorie limitation is a non-genetic process that is proposed to slow down aging in mammals (Dirks and Leeuwenburgh 2006). Moreover, it is known as calorie intake lowering while maintaining the fundamental alimentary demanding. The mammalian experimental calorie restriction by decreasing calorie intake by ~40% led to the life extension of animals by 30%–40% (Weindruch et al., 1986).

How calorie restriction is can significantly extend the life span? It is probably due to some modifications in a number of molecular, cellular, and systemic processes that lead to not only a long life span, but also increase in the metabolism, neuroendocrine, immune, and collagen responses (Mobbs et al., 2001). These alterations can be controlled by variations in gene expression profiles, as well as metabolic reprogramming by a transcriptional process probably caused by insulin due to 1) lowering energy metabolism, and 2) greater biosynthesis and rotation of proteins (Weinert and Timiras 2003).

Even if the short-term influences in humans are favorable (Fontana et al., 2004), short-term researches are not unexpected hard to behavior in humans. The lack of information about human samples is fundamental may be lead to fierce opposition by this toughs involvement and the length of the human life span.

Many research showed that the Okinawan people are differentiated by low morbidity and mortality have the longest percentages of life span in the world, maybe due to healthy nutrition and a decreased caloric intake. Regardless of the

considerable information indicating the beneficial effect of calorie restriction on health and delaying the aging in animal samples, it is probable that these useful effects be missed in the generalization to human samples (Dirks and Leeuwenburgh 2006). As a result, it could be shown that the antecedent major probability around the large-term caloric limitation as to the fresh "fountain of youth" has newly been resized.

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