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Review

Regulation and protection of mitochondrial physiology by sirtuins

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ABSTRACT

The link between sirtuin activity and mitochondrial biology has recently emerged as an important field. This conserved family of NAD^+-dependent deacetylase proteins has been described to be particularly involved in metabolism and longevity. Recent studies on protein acetylation have uncovered a high number of acetylated mitochondrial proteins indicating that acetylation/deacetylation processes may be important not only for the regulation of mitochondrial homeostasis but also for metabolic dysfunction in the context of various diseases such as metabolic syndrome/diabetes and cancer. The functional involvement of sirtuins as sensors of the redox/nutritional state of mitochondria and their role in mitochondrial protection against stress are hereby described, suggesting that pharmacological manipulation of sirtuins is a viable strategy against several pathologies.

Contents

Abbreviations: Acetyl-CoA, acetyl-coenzyme A; AceCS2, acetyl-coenzyme A synthethase 2; ACC, Acetyl-CoA carboxylase; ADP, adenosine diphosphate; AIF, apoptosis-inducing factor; AMPK, 5′ adenosine monophosphate-activated protein kinase; ANT, adenine nucleotide translocator; ATP, adenosine triphophate; BER, base excision repair; CPS1, Carbamoyl phosphate synthase; CR, calorie restriction; CREB, cAMP response element-binding; CypD, cyclophilin D; DNA-PK, DNA-dependent protein kinase; DSB, double-strand break; ERR α, Estrogen-related receptor alpha; FAO, fatty acid oxidation; FOXO, Forkhead box O; GDH, glutamate dehydrogenase; H4, histone 4; HDL, high-density lipoprotein; HFD, high fat diet; HIF1α, Hypoxia-inducible factor 1, alpha subunit; HMGCS2, 3-hydroxy-3-methylglutaryl CoA synthase 2 Km, Michaelis-Menten constant; LCAD, long chain acyl coenzyme A dehydrogenase; MEFs, mouse embryonic fibroblasts; MPP, mitochondrial processing peptidase; mPTP, mitochondrial permeability transition pore; MnSOD, manganese superoxide dismutase; NAD^+, nicotinamide adenine dinucleotide; NDUFA9, NADH dehydrogenase [ubiquinone]-1 alpha subcomplex subunit; OSCC, oral squamous cell carcinoma; OTC, ornithine transcarbamoylase; PPARγ, peroxisome proliferator-activated receptor; PARP-1, Poly [ADP-ribose] polymerase 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Pol1, polimerase1; ROS, reactive oxygen species; SIRT, sirtuin; Sir2, Silent Information Regulator Two (Sir2) protein; SOD2, superoxide dismutase 2; TNF, Tumor necrosis factor; UCP2, uncoupling protein 2.

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1. Sirtuins: function and families

1.1. Introduction

The involvement of mitochondria in multiple fundamental cellular processes places these organelles under the highlight of many researchers. In fact, mitochondria are now considered one major target for many therapeutic approaches. Oxidative stress has been a particular fulcrum of interest since mitochondrial oxidative damage has been recognized as being involved in many diseases and in the aging process itself. Also, disrupted mitochondrial metabolism may be one of the critical elements leading to cancer, diabetes, age-associated and neurodegenerative disorders (Campisi and Yaswen, 2009; Harman, 1956; Sultana and Butterfield, 2010; Weber and Reichert, 2010; Zhu and Chu, 2010). In this fascinating area of mitochondrial disease and protection, sirtuins are being specially focused, since these proteins are able to regulate stress responses and cell survival (Canto and Auwerx, 2009; Gan and Mucke, 2008). One of the most intensively investigated compound, resveratrol, is a known sirtuin 1 (SIRT1) activator, shown to have a positive effect on mitochondrial metabolism and to delay the aging process (Alcain and Villalba, 2009; Finkel et al., 2009). The present review comprises our recent knowledge in the field of sirtuins with a special focus on the most recent and breakthrough studies related with the protection and regulation of mitochondrial physiology by SIRT3, SIRT4 and SIRT5. Several other reviews on the subject are available, including the very interesting work by Huang et al.(2010). The present review expands the previous works by incorporating novel and exciting results, which allows the reader to get a full picture of how sirtuins in general, and mitochondrial sirtuins in particular, contribute to cellular and mitochondrial protection.

1.2. Classification of sirtuins

Sirtuins, or Silent information regulator proteins (Sir), and their homologs are present in a very wide range of organisms, from bacteria to humans, forming a conserved family of proteins (Denu, 2005). Up to date, seven sirtuin homologues have been identified in mammalian cells. These have different intracellular localization as well as various roles in cell physiology (Blander and Guarente, 2004; Tanny et al., 1999). Based on the phylogenetic analysis of the core domain, mammalian sirtuins have been classified into four classes together with other Sir2-related proteins widely distributed in eukaryotes and prokaryotes (Frye, 2000; Smith et al., 2000). Mammalian SIRT1 (62.0 kDa), SIRT2 (41.5 kDa) and SIRT3 (43.6 kDa) are considered Class I sirtuins, while SIRT4 (35.2 kDa) is a Class II sirtuin. Class III SIRT5 (33.9 kDa) and Class IV SIRT6 (39.1 kDa) and SIRT7 (44.8 kDa) are other examples. All the described sirtuins contain a conserved 275 amino acid catalytic core domain together with N-terminal and/or C-terminal domains. Additionally, a novel class ("U") has been created to include sirtuins with unique features, such as gram-positive bacteria and *Termoga maritime* sirtuins. An appropriate Class affiliation of the individual Sir2-related proteins has been described in the comprehensive review article by Michan and Sinclair(2007). A list of the different sirtuins, plus other details on their physiology/activity, can be seen in Table 1.

1.3. Sirtuin enzymatic activity

All sirtuins, with only one exception (SIRT4), catalyze protein deacetylation in which the lysine acetyl group is transferred from the target protein to the ADP-ribose component of NAD^+, which leads to their full dependence on NAD^+ availability and indicates that sirtuins can be sensors of the cellular redox state. As a consequence, sirtuin activity leads to the generation of deacetylated proteins, 2′-O-acetyl-ADP ribose and nicotinamide (Sauve, 2010). Moreover, SIRT6 additionally demonstrates ADP-ribosyl transferase activity while SIRT4 (as mentioned earlier) demonstrates ADP-ribosyl transferase activity only. As described above, sirtuin activity is regulated by NAD^+ availability. On the other hand, nicotinamide noncompetitively inhibits sirtuins suggesting that the deacetylation reaction product can also act as an endogenous regulator of sirtuin activity. Interestingly, isonicotinamide, which binds to the nicotinamide pocket of yeast sirtuin (Sir2), only inhibits the base exchange, with the deacetylation activity remaining unaffected or even being increased. This fact indicates that chemical compounds such as isonicotinamide can act as potent sirtuins activators in mammalian cells. Additionally, it has been demonstrated that activity of yeast sirtuin Hst2 (a Class I member) can be regulated by homo-oligomerization of the enzyme. Another well known and currently intensively studied sirtuin activator is resveratrol, a polyphenol present in different sources, including for example grapes skin and red wine (Lagouge et al., 2006). It has been demonstrated that polyphenols and especially resveratrol, reduce K_m values for sirtuin substrates, resulting in different biological effects as increased resistance to apoptosis and to stress stimuli. Apart from nicotinamide, an inhibitory effect on sirtuins has also been described for several other compounds. The most well-known are sirtinol, splitomicin (specific for yeast sirtuins Hst1 and Sir2) and dehydrosplitomicin (specific mostly to sirtuin Hst1). Human sirtuins are not inhibited significantly by splitomicin as well as by dehydrosplitomicin. More about the mechanism of protein deacetylation carried out by sirtuins as well as detail on their inhibitors and activators can be found in the review of Sauve et al. (Sauve et al., 2006).

1.4. Sirtuin protein targets

Potential sirtuins substrates are various acetylated proteins involved in cell metabolism, apoptosis and regulation of gene transcription. Sirtuins can thus determine the ability of cells to adapt to different conditions (Finkel et al., 2009; Haigis and Guarente, 2006; Vaquero, 2009). Published data suggest a significant role of deacetylation in metabolic responses to fasting or caloric restriction as well as in the response to different stress stimuli, including for example oxidative stress (Choudhary et al., 2009; Schwer et al., 2009). Among the several proteins which are deacetylated by sirtuins, histones and transcription factors such as p53 (Li et al., 2010), FOXO (Brunet et al., 2004), peroxisome proliferator activated receptor γ (PPARγ) (Picard et al., 2004), nuclear factor-κB (NFκB) (Kawahara et al., 2009) and PGC-1α (Sugden et al., 2010) can be found. Sirtuins are also able to deacetylate α-tubulin (Tang and Chua, 2008) and acetyl-CoA synthetase (Hallows et al., 2006). Another important protein for metabolism, glutamate dehydrogenase (GDH) is a well-known example of ADP-ribosylation substrates for SIRT4 (Haigis et al., 2006). The variety of sirtuin substrates, either being crucial enzymes or gene regulatory elements, indicates the possibility that multiple sirtuins may modulate cell physiology and metabolism through interacting with distinct targets regulated under a wide range of physiological conditions.

1.5. Tissue specificity and intracellular localization of mammalian sirtuins

Molecular analysis revealed that SIRT1, 2, 3, 5 and 6 are ubiquitously expressed in different tissues and organs. The highest amount of SIRT6 was detected in muscles, brain and heart, while SIRT4 is mostly present in muscle, kidney, testis and liver (Michishita et al., 2005). By its turn, SIRT7 has been found in brain, kidney, liver, lung and adipose tissue (Michishita et al., 2005). Further detailed studies determined subcellular localization of several sirtuins. Among seven mammalian sirtuins, SIRT1 and SIRT2 show both cytoplasmic and nuclear localization, while SIRT6 and SIRT7 are only located in the nucleus and nucleoli, respectively (Michishita et al., 2005). SIRT3, SIRT4 and SIRT5 are mitochondrial proteins, although SIRT3