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Review Article

Redox-regulating sirtuins in aging, caloric restriction, and exercise

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ABSTRACT

The consequence of decreased nicotinamide adenine dinucleotide (NAD^+) levels as a result of oxidative challenge is altered activity of sirtuins, which, in turn, brings about a wide range of modifications in mammalian cellular metabolism. Sirtuins, especially SIRT1, deacetylate important transcription factors such as p53, forkhead homeobox type O proteins, nuclear factor κB, or peroxisome proliferator-activated receptor γ coactivator 1α (which controls the transcription of pro- and antioxidant enzymes, by which the cellular redox state is affected). The role of SIRT1 in DNA repair is enigmatic, because it activates Ku70 to cope with double-strand breaks, but deacetylation of apurinic/apyrimidinic endonuclease 1 and probably of 8-oxoguanine-DNA glycosylase 1 decreases the activity of these DNA repair enzymes. The protein-stabilizing effects of the NAD+-dependent lysine deacetylases are readily related to housekeeping and redox regulation. The role of sirtuins in caloric restriction (CR)-related longevity in yeast is currently under debate. However, in mammals, it seems certain that sirtuins are involved in many cellular processes that mediate longevity and disease prevention via the effects of CR through the vascular, neuronal, and muscular systems. Regular physical exercise-mediated health promotion also involves sirtuin-regulated pathways including the antioxidant-, macromolecular damage repair-, energy-, mitochondrial function-, and neuronal plasticity-associated pathways. This review critically evaluates these findings and points out the age-associated role of sirtuins.

Contents

Abbreviations: 8-oxoG, 8-oxo-7, 8-dihydroguanine; APE1, apurinic/apyrimidinic endonuclease 1; BER, DNA base excision repair; CR, caloric restriction; DSB, DNA double-strand break; FOXO, forkhead homeobox type O protein; eIF2α, eukaryotic initiation factor 2α; eNOS, endothelial nitric oxide synthase; IL-1β, interleukin 1β; OGG1, 8-oxoguanine-DNA glycosylase 1; PIG3, p53-induced gene 3; PARP1, poly(ADP-ribose) polymerase 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; MST1, mammalian sterile 20-like kinase 1; NAD+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; NOXA, NADPH activator A; SIRT1, sirtuin (silent mating type information regulation 2 homolog) 1 or NAD+-dependent deacetylase sirtuin 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2; Sir2, silent information regulator 2; TNF-α, tumor necrosis factor α; Trx, thioredoxin; UCP2, uncoupling protein 2

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Introduction

Sirtuins (silent information regulator 2 (Sir2)1 proteins) belong to an ancient family of evolutionarily conserved NAD^+-dependent enzymes with deacetylase and/or mono-ADP-ribosyltransferase activity and are implicated in diverse cellular processes. The sirtuin family is ubiquitously distributed in mammals, with seven homologs (SIRTs 1–7), and their expression/activity shows organ and organelle specificity. Powerful protein deacetylase activity of SIRT1, SIRT2, SIRT3, and SIRT5 has been reported toward histones, whereas SIRT4, SIRT6, and SIRT7 have no such detectable enzymatic activity on histone peptide substrate [1,2]. SIRTs 3–5 are predominantly localized to the mitochondria. Mammalian sirtuins are closely involved in metabolism [2–4], which is linked to the mitochondrial generation of reactive oxygen species (ROS) [5,6]. SIRT1 is downstream in ROS signaling because of a dependence on the availability of NAD, but it can be important upstream in cellular regulators, including forkhead homeobox type O factor 3 (FOXO3) [7], muscle-specific RING finger protein 1 [8], and the v-Akt murine thymoma viral oncogene homolog 1 (Akt1) [9].

The crystal structure of human SIRT1 (a homolog of yeast Sir2) reveals a large groove intersected by a pocket lined with hydrophobic residues, conserved with class-specific protein-binding sites of each Sir2 class [10]. Activity of most of the sirtuins is controlled by posttranslational modifications, as well as the availability of NAD^+. It has been shown that they are phosphorylated at N- and C-terminals, which play a role in substrate binding [11]. Moreover, in addition to phosphorylation, it appears that S-nitrosylation of SIRT1 impairs the catalytic activity of enzymes via a nitrosylated glyceraldehyde-3-phosphate dehydrogenase-mediated process [12]. Additionally, thioredoxin (Trx) regulates cellular redox balance through reversible oxidization of its redox-active cysteine residues (-Cys-Gly-Pro-Cys-), which can mediate protein S-denitrosylation [13–15] and hence the activity of sirtuins. The deacetylase domain of sirtuins consists of approximately 250 amino acids, differentiated by divergent N- and C-terminal extensions [16]. In the budding yeast Saccharomyces cerevisiae, the Sir proteins are involved in a wide array of cellular processes, including the nonhomologous end-joining repair of DNA [17], the stabilization of the replication forks in the ribosomal (r) DNA to prevent DNA breaks, recombination, and the generation of extrachromosomal rDNA circles [18], which leads to aging of this organism [19].

One of the first studies that linked sirtuins to aging was based on the observation that proteins encoded by SIR genes are responsible for silencing the rDNA of S. cerevisiae [20]. The same group of investigators also demonstrated that Sir2 is redox sensitive because of its NAD^+ dependence. Moreover, they showed that sirtuins have deacetylase activity from eubacteria to humans [21]. Guarente and his group then demonstrated that redistribution of the Sir2 complex from a telomere to the nucleolus is associated with aging in yeast [19,22], and overexpression of this gene extends their life span [23]. Sinclair and co-workers showed that life extension in yeast could be done via the salvage pathway of NAD^+ [24], and life-span extension during caloric restriction (CR) is associated with activation of Sir2 genes in yeast and the mammalian homolog SIRT1 of human cells [25,26]. Now, mounting data suggest an active role for sirtuins in aging and age-associated diseases. However, as with most phenomena in science, the convincing effects of sirtuins in mammalian aging are not without debate [27].

This paper reviews the redox sensitivity of sirtuins and the role of these lysine deacetylases, especially SIRT1, in the aging process. The authors also crucially review the data of knockout and overexpression models, as well as the effects of CR and physical exercise. The effects of resveratrol, which is a potent stimulator of SIRT1, have been reviewed elsewhere [28–31].

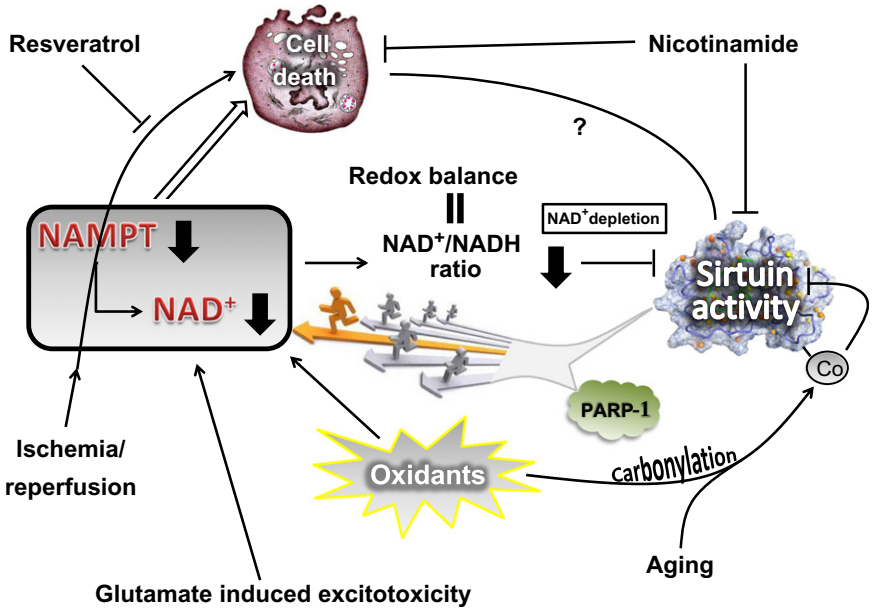

Fig. 1. The suggested mechanisms between the availability of NAD and the activities of sirtuins and PARP is shown. Metabolic challenges modulate NAD levels, NAD:NADH ratio, and cell fate by shifting to either pro- or antiapoptotic pathways.