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Review Article

The role of sirtuins in aging and age-related diseases

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ABSTRACT

Sirtuins, initially described as histone deacetylases and gene silencers in yeast, are now known to have much more functions and to be much more abundant in living organisms. Sirtuins gained much attention when they were first acknowledged to be responsible for some beneficial and longevity-promoting effects of calorie restriction in many species of animals – from fruit flies to mammals. In this paper, we discuss some detailed molecular mechanisms of inducing these effects, and wonder if they could be possibly mimicked without actually applying calorie restriction, through induction of sirtuin activity. It is known now that sirtuins, when adjusting the pattern of cellular metabolism to nutrient availability, can regulate many metabolic functions significant from the standpoint of aging research – including DNA repair, genome stability, inflammatory response, apoptosis, cell cycle, and mitochondrial functions. While carrying out these regulations, sirtuins cooperate with many transcription factors, including PGC-1a, NFKB, p53 and FoxO. This paper contains some considerations about possible use of facilitating activity of the sirtuins in prevention of aging, metabolic syndrome, chronic inflammation, and other diseases.

Contents

1. Introduction

Sirtuins are orthologues of yeast Sir2 protein, where SIR stands for "silent information regulator", because in yeast, where Sir2 was first discovered, the protein silences certain genes (i.e. inhibits their expression), which results in the extension of replicative lifespan.

Sirtuins attracted some attention of researchers when it was presumed that inducing their activity may be responsible, or at least co-responsible for lifespan-extending effects of calorie restriction (i.e. anti-inflammatory effects, improved glucose tolerance, inhibition of hepatic steatosis and other degenerative disorders, as well as for improved endothelial function, regression of atherosclerotic plaques, and cancer prevention). It was also discovered that pharmacological induction of sirtuin activity can mimic beneficial effects of calorie restriction without actually

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applying calorie restriction. On the other hand, segmental inhibition of sirtuin activity might find some therapeutic use in future, mainly because of its proapoptotic effects in cancer cells, and inhibitory effects on proliferation of parasitic protozoa and human cells infected with viruses.

Initial hopes associated with the discovery of sirtuins [1]:

The findings concerning effects of calorie restriction, extending lifespan of many animal species, aroused presumptions that some molecular mechanisms underlying this beneficial effect may be shared and evolutionarily conserved. In 1998, research studies on *Sacharomyces cerevisiae* showed that gain of function of Sir2 gene results in changes of cellular metabolic pattern, involving – among others – epigenetic silencing of certain genes, improved genomic stability, and extension of the replicative lifespan [2].

In yeast, unequal division of cell content between the budding cell and the budded cell allows defining maximal lifespan on the basis of maximal number of cells which can be budded from a single cell before its death [3]. One of the factors limiting replicative lifespan in yeast cells is accumulation of rDNA circles (i.e. DNA fragments encoding rRNA) in their genome. Such circles can be removed through recombination, but for some reasons they are preferentially left in the budding parental cell [4], which finally results in its death, though the exact underlying mechanism is still unknown. It is known, however, that gain of function of Sir2 extends yeast replicative lifespan indeed through suppressing formation of the rDNA circles in the genome.

Since the gain of function of Sir2 orthologues in *Caenorhabditis elegans* and *Drosophila melanogaster* also extends their lifespan [5,6], accumulation of the rDNA circles has been excluded as a mechanism of aging in those organisms. Therefore, it has been presumed that lifespan-extending effect of Sir2 (or its orthologue) amplification need not be determined by any definite molecular mechanism of action. Yet, its general beneficial effect on lifespan has been conserved (i.e. adjusted to organism-specific processes responsible for aging, regardless of their exact molecular pattern). Because calorie restriction (CR) has also shown such species-independent beneficial effect on lifespan, and CR was found to result in Sir2 upregulation in yeast, sirtuin activation is presumed to be a significant mechanism, or at least one of the significant mechanisms underlying longevity-promoting effects of CR [7]. A possible mechanism of CR action can be inhibition of insulin and IGF-dependent signaling (IIS), simply through decreasing tissue demand for insulin and IGFs, and correspondingly – secretion of those hormones [8]. During CR, IIS pathway inhibition coexists with the altered expression of sirtuins in various tissues. In *C. elegans*, CR generally stimulates Sir2 expression, but in mammals CR effects are more complex, in both tissue- and particular sirtuin-dependent manner [9]. According to some authors, gain in sirtuins activity seems to be a result of decreased ubiquitination (and hence – decreased degradation), not of increased synthesis [10]. However, additional cross-talk between inhibition of IIS pathway and enhanced activity of some sirtuins can exist (e.g. SIRT6 downregulates c-Jun, which is one of the crucial downstream effectors of IIS pathway; while miRNA encoded in an introne of sterol-regulatory element binding protein 1 (SREBP-1) gene down-regulates SIRT6 translation [11,12]). Hence, existence of more than one mechanism underlying beneficial effects of CR is possible. Moreover – several CR induced mechanisms can complement one another.

Not all laboratories managed to repeat the initial lifespan-extending effect of sirtuins upregulation (e.g. positive correlation between SIRT3 activity and human healthspan, initially described for Italian population, was not confirmed in later studies on other populations) [13,14]. Despite the existence of straightforward correlation in *C. elegans* or fruit flies, sirtuin upregulation in mammals can work in a context-, tissue-, and particular sirtuin-dependent manner (e.g. 12-fold increase in SIRT1 activity in mice was neuroprotective, though it induced cardiac hypertrophy) [15]. Furthermore, studies on SIRT KO mice show a lifespan shortening only as a result of depletion of some sirtuins (SIRT3, SIRT6, SIRT7) but not others (SIRT5) [16]. Despite those controversies as to whether the calorie restriction indeed extends lifespan in all animal species [17], lack of its beneficial effect in Sir2 knock-out organisms [18] seems to support the hypothesis claiming that the lifespan-extending effect of CR can really consist in activation of some sirtuins.

Regardless of whether sirtuins do extend lifespan or not, recent studies on mice have shown that sirtuin modulation may have a beneficial effect on health, alleviating manifestations of many diseases, including diabetes, metabolic syndrome, cardiomyopathies, non-alcoholic hepatic steatosis, hyperinsulinism-induced dyslipidemia, chronic inflammation, neurodegenerative diseases, and some types of cancer. [19,20]

2. Review

2.1. Sirtuins are NAD^+-dependent lysine deacetylases

During the deacetylation catalyzed by sirtuins, a cleavage of chemical bond between nicotinamide and ribose in NAD^+ molecule is coupled with the transfer of acetyl group from the substrate (i.e. acetylated lysine residue) to ribose within the remaining ADP-ribose molecule. The final products of the reaction are: deacetylated lysine residue, O-acetyl-ADP-ribose, and nicotinamide [21]. Thus, sirtuin activity may be determined by the quantity of sirtuin molecules, availability of NAD^+ (as a co-substrate), and local concentration of nicotinamide which inhibits sirtuin activity (as a product, within the frames of end product inhibition). In addition, sirtuin activity may be influenced by other intracellular proteins [22,23].

The NAD^+ concentration in cells is maintained by keeping balance between its synthesis and its use. In humans, NAD^+ can be obtained from the tryptophane, nicotinic acid, or nicotinamide ribose [24]. Synthesis of the new NAD^+ molecules occurs mainly in the course of tryptophane metabolism through kynurenine pathway, as a result of eight reactions, each of them highly conserved in the course of evolution. In yeast, the activity of this pathway is regulated by other yeast sirtuin, Hst2, which serves as a sensor of NAD^+ concentration in the cell, and in case of too high concentration inhibits activity of kynurenine pathway [25]. It has been shown that in mammals SIRT1 can modulate NAD^+ biosynthesis, especially through salvage pathway, consisting in NAD^+ resynthesis from nicotinamide [26,27]. The biggest consumers of NAD^+ in the cell include mono-ADP-ribosyltransferases and poly-ADP-ribosyltranferases, which break glycozidic bond within NAD^+ molecules, and subsequently transfer ADP to other substrates. The DNA repairs, especially the repair of double strand breaks (DSB), requires intense activity of poly-ADP- ribose polimerase (PARP) and sometimes may adversely result in a critical loss of NAD^+ concentration in a cell [28].

Salvage pathway can prevent cellular NAD^+ depletion through re-synthesizing NAD^+ from nicotinamide [1]. Moreover, this can also induce the sirtuin activity by lowering the level of nicotinamide [29–31]. The key enzyme on this pathway is nicotinamide phosphoribosyltransferase (NAMPT) which has been shown to affect both the NAD^+ concentration in cells and the sirtuin activity [29–31]. It has been shown recently that NAMPT expression is regulated by transcription factors related to diurnal activity, which can affect diurnal oscillation of both the NAD^+ concentration and sirtuin activity in cells [26,27].