

Sirtuins and Aging: is there a Role for Resveratrol?

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Abstract Prolonged human life duration is consequently associated with a higher incidence of chronic diseases. Aging is a very complex process in which genetic, environmental and cellular pathways are involved. Along with aging, longevity has been linked with Sirtuins. Sirtuin enzymes are a family of highly conserved protein deacetylases that have been linked with calorie restriction and aging by modulating energy metabolism, genomic stability and stress resistance. Aim of this brief review is to describe Sirtuins' influence on the conditions that worsen the physiological aging. We will also report the beneficial effects of the polyphenol resveratrol on these molecules and the possible therapeutical perspectives.

Keywords *Resveratrol; Aging; Sirtuins*

1. Introduction

The growing interest of scientists and researchers about aging may be also explained if we consider that the prolonged human life duration is consequently associated with increasing costs of public health due to the higher incidence of chronic diseases like diabetes, kidney failure, hypertension, neurodegenerative diseases, osteoporosis and cancer. From this point of view the future health challenge is to provide people with a better aging without excessive health costs.

At the date, if you type on PubMed screen the query "aging", more than 330000 results will be shown. Modern societies, especially the western ones, are aging due to the prolonged life span, the reduced birth rates and the technological and scientific advances.

Different hypotheses have been postulated to explain aging and its underlying mechanisms. We actually know that it is a very complex process in which genetic, environmental and cellular pathways are involved. Among these, oxidative stress was widely investigated for its tight implications in vascular aging that plays a key role in this process. In fact, cardiovascular and cerebrovascular events are significantly more frequent in aging adults [1].

Along with aging, longevity was largely focused. Caloric restriction (CR) is a nutritional technique used in different models as a healthy method to prolong lifespan [2] through a reduction of calorie intake by 30-40% but avoiding malnutrition. This method's effects could be mediated by Sirtuins.

2. Sirtuins

Sirtuin enzymes are a family of highly conserved protein deacetylases that depend on nicotinamide adenine dinucleotide (NAD⁺) for their activity. Sirtuins catalyze the removal of acetyl groups from lysine residues. They may promote different post translational modifications in a wide range of proteins so they are actually defined as deacylases [3].

Seven Sirtuins have been actually identified in mammals, listed from 1 to 7. Each of them exhibits a catalytic domain present in all Sirtuins whilst different N- and C- ends give to these proteins their characteristic biological properties.

They have distinct subcellular localizations: SIRT1, 6 and 7 are nuclear; SIRT2 is cytosolic whilst SIRT3, 4 and 5 are primarily located in mitochondria [4]. Among these proteins, only SIRT4 has no a known deacetylation substrate [5].

Sirtuins were originally investigated in yeast and they have been linked with calorie restriction and aging by modulating energy metabolism, genomic stability and stress resistance [6]. SIRT4 and SIRT6 also exhibit ADP-ribosyl-transferase activity [7].

For each of the formerly mentioned chronic diseases, a direct or indirect role of one or more Sirtuins has been demonstrated.

Aim of this brief review is to describe Sirtuins' influence on the conditions that worsen the physiological aging. We will also report the beneficial effects of the polyphenol resveratrol on these molecules and the possible therapeutic perspectives.

3. Sirtuins, Glucose Metabolism and Kidney Disease

In animal models, SIRT1 influences glucose-dependent insulin production in pancreatic beta-cells [8, 9] whose proliferation is negatively regulated by the same Sirtuin. Mitochondrial SIRT4 inhibits insulin secretion in response to aminoacids. In insulinoma cells an overexpression of SIRT4 has been demonstrated, thus leading to a decreased insulin synthesis as a reaction to blood glucose concentration [3].

In the liver SIRT1 promotes gluconeogenesis and blunts glycolysis via deacetylation of PGC-1 α (PPAR- γ coactivator-1 α) [10].

The same deacetylase enhances insulin sensitivity by modulating insulin signalling [11], inhibits fat storage and stimulates fatty acids release in white adipose tissue [12].

Transgenic overexpression of SIRT1 not only prevents diabetes in animal models, but also dulls diabetes that occurs during normal aging [13, 14]. Similarly, chemical activation of SIRT1 has antidiabetic and other beneficial effects. SRT1720 is one of potential SIRT1 activators being examined in clinical trials.

Recently also SIRT6 has been proved to be involved in metabolic control: in fact, its absence is likely related to an enhancement of insulin signalling with consequent hypoglycemia [15]. With its histone

deacetylase activity, Sirt6 regulates the glucose levels through the blockade of different glycolytic genes [16].

This is more interesting if we consider the high incidence of diabetes and its complications among which diabetic nephropathy plays a leading role as a major determinant of morbidity and mortality [17]. A protective effect of Sirtuins in kidney is widely demonstrated by different mechanisms: they blunt hypoxia, reduce fibrosis, inhibit apoptosis and inflammation, reduce autophagy and modulate blood pressure [18]. For what concerns the last item, SIRT1 acts through the regulation of vascular tone and the handling of renal sodium in the collecting duct [19, 20].

Moreover, SIRT3 attenuates lipotoxicity and ROS-related inflammation in proximal tubular cells, thus underlining the protective role of these molecules against oxidative stress in its multiple tissue expression [21]. SIRT3 is also able to regulate fatty acids metabolism and promotes lipid catabolism by deacetylating various mitochondrial proteins [22].

4. Sirtuins, DNA Stability, Oxidative Stress and Cancer

Aging is accelerated by DNA damage. Sirtuins rescue this damage. SIRT1, one of the most investigated in this field, can deacetylate several factors involved in DNA repair and genomic stability [23].

Also SIRT6 plays a role in genome stabilization, gene expression and DNA repair. Its deacetylation activity reduces chromosomal instability which is a fundamental feature of human cancer cells [24]. On the other hand, SIRT6 allows repair factors to reach chromatin thus minimizing DNA damage [25]. SIRT6 chromosomal locus is frequently broken in human acute myeloid leukemia [26]. In addition, the same deacetylase influences transcriptional activity through the inhibition of NF- κ B target genes, especially those associated with aging [27]. It is known that NF- κ B is a central factor for aging, inflammation, immunity and cell proliferation; for many authors this is the link between all these conditions and aging.

Oxidative stress, along with other factors, is involved in chronic obstructive pulmonary disease (COPD) which is associated, on its turn, with the premature lung senescence. SIRT6 is significantly decreased in lung of patients with severe COPD [28]. In this clinical condition, NF- κ B regulates the expression of genes for proinflammatory molecules [29].

We know that ROS may damage nucleic acids, thus eliciting the onset of cancer (whose incidence grows in elder). In animal models the lack of SIRT3 is associated with greater genomic instability and increased sensitivity to oncogenic transformation if compared with controls [30].

The protective role of SIRT3 is also suggested by the observation that several human neoplastic tissues exhibit reduced SIRT3 levels when compared with healthy tissues [30]. Overexpression of the same Sirtuin suppresses cancer proliferation by inhibiting the activity of Hypoxia Inducible Factor-1- α (HIF-1- α) [31, 32]. It is interesting to underline that this factor is activated and stabilized by ROS thus strengthening the role of oxidative stress.

From the study of different human tumours, SIRT3 emerges as a powerful, cell-specific and very complex tumor suppressor [33].

As a further demonstration of its antioxidant activity, in mice SIRT3 delayed the age-related hearing loss by enhancing mitochondrial antioxidant defenses [34].

As mentioned above, SIRT1 is the most investigated about its possible relationship with cancer, but only SIRT7 has been seriously linked with different cancer types. In fact, it has been found to be overexpressed in tumours originating from thyroid, breast, bladder, liver and colon, thus leading to the working hypothesis that it could be a potential oncogene [35].

5. Sirtuins and Neurodegenerative Diseases

In light of the former considerations, it's easy to understand that Sirtuin enzymes are potential therapeutic targets in several human diseases including cancer, diabetes, inflammatory disorders and neurodegenerative diseases.

In fact it is reasonable to hypothesize that a selective modulation of a single Sirtuin could beneficially affect different clinical conditions. For example, SIRT6 is an attractive target for the prevention and treatment of inflammatory, cardiovascular and pulmonary diseases [5].

Modulation of Sirtuin activity has been shown to impact the course of several aggregate-forming neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and spinal and bulbar muscular atrophy.

Lewy bodies are frequently found in many of these disorders and consist of protein inclusions whose major constituent is α -Synuclein (α -Syn), a presynaptic neuronal protein that besides the brain is widely expressed in other tissues. This protein has been pointed out to be a target of cellular protein quality control whose activity is impaired by aging thus causing neurodegeneration. On the other hand, the same protein could influence the protein quality control system. Sirtuins can influence the progression of neurodegenerative disorders by modulating transcription factor activity and directly deacetylating proteotoxic species, especially the ones involved in autophagy degradation pathway [36].

6. Sirtuins and Resveratrol

Further research is needed but on our opinion Sirtuins could become an interesting and powerful target to treat many human diseases.

At this regard we would like to underline the potential role of resveratrol, a natural Phytoalexin compound, which was extensively studied for its antioxidant and radicals' scavenging properties. More recently, this polyphenol has been shown to interact also with Sirtuins and from these complex (direct and indirect) interactions a putative therapeutical role for many of the above mentioned diseases could arise.

It is a common observation that a healthy diets associated with a delayed onset of stroke and neurological diseases. Regular consumption of fruit, vegetables and fish reduces the risk of cognitive decline in the elderly population. Old people who regularly drink red wine exhibit a reduced (up to 50%) risk of developing dementia [37]. These neuroprotective effects of resveratrol could be partially mediated by SIRT1 activation and scavenging activity. Moreover Resveratrol could influence amyloid generation and clearance [38]. However, Resveratrol's poor absorption and availability (less than 1%) in human it is well known, besides its fast metabolism [39]. Biotechnology is actually working to develop different formulations (e.g. nanocapsules) that could provide a higher dose of resveratrol without eliciting its side effects (frequently nausea and diarrhea) [40]; daily doses less than 1g are generally considered safe. Resveratrol is able in lowering blood glucose levels via an increase in GLP-1 production in mice. More recently, in type 2 diabetic subjects supplemented with a daily resveratrol dose at 10 mg, Brasnyo and coworkers [41] observed an improvement of insulin sensitivity, a reduction in oxidative stress and in postprandial glucose spike. In subjects with metabolic

syndrome treated with resveratrol for six months improved flow-mediated dilation was observed and this beneficial effect disappeared when resveratrol treatment was stopped [42]. In diabetics resveratrol supplement for three months was associated with a better fasting blood glucose, blood pressure, triglycerides and LDL cholesterol levels if compared with subjects with a standard antidiabetic treatment [43].

For a better understanding of resveratrol effects in humans, we have to say that trials are not really comparable for sample size, aims, methods and resveratrol dose but we can say that resveratrol is a powerful SIRT1 activator, may be directly. This activation, on its turn, induces deacetylation and suppresses the activity of the Foxo1 transcription factor which is involved in insulin signaling due to its inhibitory role in glucose uptake and utilization in skeletal muscle [44]. This is interesting if we consider that aging and diabetic subjects usually exhibit a significant reduction in skeletal muscle mass and strength thus worsening the sedentary way of life that is typically observed in these people and that contributes to make these subjects more prone to obesity and its complications.

The same SIRT1/Foxo1 axis has been recently postulated to be involved in cardiac aging. In fact heart performance decreases with age and Foxo1-related apoptotic signalling increases. A long term treatment with resveratrol improves cardiac function in senescent mice also by reducing age-induced deposition of collagen fibers [45].

Besides the well-known antioxidant effects, resveratrol could be a promising natural approach to many of the age-related disorders.

In our previous papers we suggested that a moderate and regular wine consumption, in the wide frame of Mediterranean diet, could be useful to prevent and treat cardiovascular, metabolic and renal disorders [46-49].

Recently, Russo and coworkers [51] proposed Sirtuins-resveratrol axis as a model to deeply investigate the beneficial effects of the Mediterranean diet: in fact this food regimen positively influences microbioma composition and stem cell function by means of the activity of many useful components, resveratrol included.

Many efforts are needed to better understand these molecular mechanisms but it is reasonable to hypothesize that a similar advice could be suggested to delay the onset of aging and its complications.

7. Conclusion

Many efforts are needed to better understand these molecular mechanisms but it is reasonable to hypothesize that a similar advice could be suggested to delay the onset of aging and its complications. From this point of view, dietary and lifestyle interventions could be useful instead of drugs thus significantly saving public resources.

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