A Review of the Sirtuin System, its Clinical Implications, and the Potential Role of Dietary Activators like Resveratrol: Part 2

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Abstract
The silent information regulator (SIR) genes (sirtuins) comprise a highly conserved family of proteins, with one or more sirtuins present in virtually all species from bacteria to mammals. In mammals seven sirtuin genes – SIRT1 to SIRT7 – have been identified. Emerging from research on the sirtuins is a growing appreciation that they are a very complicated biological response system that influences many other regulator molecules and pathways in complex manners. Part 1 of this article provided an overview of the mammalian sirtuin system, discussed the dietary, lifestyle, and environmental factors that influence sirtuin activity, and summarized research on the importance of vitamin B3 in supporting sirtuin enzyme activity, as well as the role specifically of the amide form of this vitamin – nicotinamide – to inhibit sirtuin enzyme activity. In Part 2 of this review, clinical situations where sirtuins might play a significant role, including longevity, obesity, fatty liver disease, cardiovascular health, neurological disease, and cancer are discussed. Research on the ability of nutritional substances, especially resveratrol, to influence sirtuin expression and function, and hence alter the courses of some clinical situations, is also reviewed. *(Altern Med Rev* 2010;15(4):313-328)

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Introduction

The silent information regulator (SIR) genes (sirtuins) comprise a highly conserved family of proteins, with one or more sirtuins present in virtually all species from bacteria to mammals. In mammals seven sirtuin genes – SIRT1 to SIRT7 – have been identified. These seven sirtuin genes code for seven distinct sirtuin enzymes that act as deacetylases or mono-ADP-ribosyltransferases. All sirtuin enzymes are dependent on oxidized nicotinamide adenine dinucleotide (NAD^+).

As was discussed in Part 1 of this review, sirtuins: (1) are genes that control other genes, (2) respond in an epigenetic manner to a variety of environmental factors, and (3) are hypothesized to play a particularly important role in an organism's response to certain types of stress and toxicity. Because of this, sirtuins have drawn interest for situations, including lifespan extension, age-related disorders, obesity, heart disease, neurological function, and cancer. This article reviews research on specific clinical situations where sirtuins may potentially play a role. Research on exogenous methods of influencing sirtuins, such as resveratrol, will also be explored.

Anti-aging (Lifespan Extension)

The sirtuin system appears to be involved in mediating the increase in longevity produced by calorie restriction. Limited available evidence also connects increased expression of SIRT1 with increased lifespan and a more gradual aging process, as well as mitigation of symptoms of aging, in some species. As an example, mice that overexpress SIRT1 have an extended lifespan and maintain lower cholesterol, blood glucose, and insulin levels. They also show increased numbers of mitochondria in their neurons.[1] Conversely, the lifespan of mice lacking SIRT1 is reduced under both normal and calorie-restricted conditions.[2] Interest in sirtuin-mediated longevity and its apparent involvement in ameliorating some age-related changes in physiology and function resulted in the discovery that resveratrol, and possibly other plant compounds, might affect these areas positively.

In vivo studies report mixed results on the lifespan extending effects of resveratrol. It has variously been reported to increase[3] or to have no detectable effect[4] on yeast lifespan. Some studies have reported increased lifespan, subsequent to resveratrol administration, in the nematode worm (*Caenorhabditis elegans*) and fruit flies (*Drosophila melanogaster*). The lifespan-extension response to

Key words: sirtuins, resveratrol, nicotinamide, niacin, vitamin B3, SIR, SIRT, longevity, anti-aging, antiaging, obesity, weight loss, fatty liver, steatosis, cancer, neurological, insulin resistance, metabolic

resveratrol appeared to be sirtuin-dependent.[5] Other research has detected no significant effects of resveratrol on lifespan increase in Drosophila or *C. elegans*.[6] While the reason for the mixed findings in yeast, nematode worms, and fruit flies is not completely clear, a study done with the fruit fly species *Anastrepha ludens* suggests that other factors might influence the response to resveratrol. In this study, resveratrol was reported to have a modest effect on lifespan in females but not males. And this effect was only observed in females when diet composition was within a very narrow range of sugar:yeast ratio, suggesting that any prolongevity benefit resveratrol might have in this species of fruit fly was both gender- and diet-dependent.[7]

Lifespan has been monitored after resveratrol was fed to fish and mammals. Adding resveratrol to the food of the short-lived seasonal fish *Nothobranchius furzeri* (a maximum recorded lifespan of 13 weeks in captivity), starting in early adulthood, produced a dose-dependent increase of median and maximum lifespan, delayed age-related decay in locomotor activity and cognitive performance, and reduction of neurofibrillary degeneration in the brain.[8] In mice, the effects of resveratrol on lifespan extension might be dependent on diet composition. Resveratrol was reported to extend the lifespan of mice when fed a high-fat diet that resulted in increased calorie consumption;[9] however, it had no significant effect in extending lifespan in trials when it was given along with a standard-chow diet.[10,11]

In the study that detected a lifespan extension effect in mice, resveratrol appeared to protect against some of the deleterious physiological effects of a high-fat diet. Compared to a standard-chow diet, a high-fat diet promotes insulin resistance, hyperglycemia, and dyslipidemia. Resveratrol feeding countered these high-fat diet induced changes. Resveratrol feeding also resulted in changes to other metabolic pathways associated with healthy aging, including reduced insulin-like growth factor-1 (IGF-1) levels, increased AMPK and PGC-1alpha activity, increased mitochondrial number, and improved motor function. These responses appear to be mediated by an epigenetic influence of resveratrol. Gene analysis revealed that a high-fat diet significantly modified the expression of 153 pathways; resveratrol opposed the effects of a high-fat diet in 144 of these.[9]

In the mice studies that did not detect lifespan extension, resveratrol still appeared to counter certain age-related changes in gene expression and physiology in a manner closely mimicking the response to calorie restriction. It induced gene expression profiles in multiple tissues, including the heart, skeletal muscle, and brain, that paralleled those induced by long-term calorie restriction.[10,11] And by old age, resveratrol-fed mice had greater bone density, aortic elasticity, and motor coordination, while also having reduced albuminuria, inflammation, and cataract formation.[11]

Limited evidence suggests that persimmon oligomeric proanthocyanidins might have lifespan-extending effects. In a mouse model of age-related dysfunction (senescence-accelerated mouse P8), administration of persimmon oligomeric proanthocyanidins extended lifespan. It also increased SIRT1 expression, suggesting that its effects on lifespan might be secondary to its impact on the sirtuin system.[12]

Quercetin has been reported to extend lifespan in *C. elegans*. While quercetin has been reported to impact the sirtuin system (discussed in Part 1), this prolongevity response does not appear to be dependent on sirtuins, but rather appears to be related to quercetin's influence on the expression of other genes in this species.[13]

Table 1. Lifespan Extension and Resveratrol

Organism	Lifespan Extension Findings
Yeast	Mixed findings
Caenorhabditis elegans (nematode worm)	Mixed findings
Drosophila melanogaster (fruit fly)	Mixed findings
Anastrepha ludens (fruit fly)	Modest effect on females that depended on diet composition
Nothobranchius furzeri (short-lived seasonal fish)	Extends lifespan
Mus species (mice)	Extends lifespan when diet is high-fat chow, but no effect on lifespan for standard chow diet

Melatonin might impact sirtuin-mediated aging effects. In senescence-accelerated mice, SIRT1 is significantly lower, as is deacetylation of some of its target proteins. These changes are associated with accelerated aging. Melatonin (10 mg/kg) added to their drinking water, starting from the end of the first month and continued until the end of the ninth month of life, increased SIRT1 and resulted in improved protein deacetylation.[14]

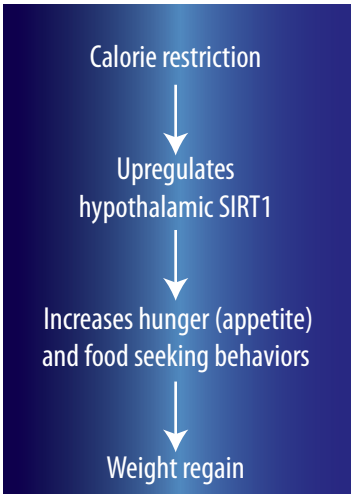
Obesity and Metabolic Syndrome

Sirtuins are thought to play a role in obesity and obesity-related issues. Evidence for this role comes from emerging understanding of the regulatory role sirtuins play in metabolic pathways and adaptations linked with obesity and aspects of metabolic syndrome. These include the expression of adipocyte cytokines (adipokines), the maturation of fat cells, insulin secretion and tissue sensitivity, modulation of plasma glucose levels, cholesterol and lipid homeostasis, and mitochondrial energy capacity.[15] SIRT1, for example, is involved in regulating the expression of adipokines such as adiponectin and tumor necrosis factor,[16-18] has been linked to hypothalamic control of energy balance,[19] plays a role in adipogenesis,[20] and is involved in the regulation of lipolysis and fatty acid mobilization in response to fasting.[20] Evidence from animal experiments where sirtuins are over- or underexpressed, and from limited human evidence, also suggests a role for sirtuins in obesity. Existing evidence on resveratrol suggests that this compound might have sirtuin-mediated anti-obesity effects.

SIRT1 is highly expressed in the hypothalamus (in the arcuate, ventromedial, dorsomedial, and paraventricular nuclei), where it appears to be involved in regulating energy homeostasis, food intake, and body weight.[19,21] Fasting upregulates hypothalamic SIRT1 expression,[21] which is associated with the fasting-induced increase in hunger, and is presumably part of the complex adaptations against calorie restriction-induced weight loss. Conversely, pharmacological inhibition of hypothalamic SIRT1 decreases food intake and body weight gain in rodents,[19] suggesting that hypothalamic SIRT1 inhibition might suppress appetite. In mice, calorie restriction induces a complex pattern of physiological and behavioral adaptations, including an increase in activity and food seeking; SIRT1 is required for these behavioral adaptations.[22]

In mice, decreased SIRT1 expression in adipose tissue is associated with obesity. In both db/db mice (leptin resistant mice) and mice that have become obese from eating a high-fat diet, SIRT1 expression in adipose tissue is low.[17] Circumstances that result in SIRT1 underexpression in white adipose enhance adipogenesis and, under fasting conditions, compromise mobilization of fatty acids from white adipocytes. Conversely, circumstances that promote white adipose SIRT1 overexpression are characterized by attenuated adipogenesis and increased lipolysis.[20]

Figure 1. Hypothalamic SIRT1 Response to Calorie Restriction: Effect on Weight Regain



Experiments with transgenic mice that were bred to moderately overexpress SIRT1 in several tissues also suggest a role for SIRT1 in protecting against obesity. Transgenic mice with greater SIRT1 expression are leaner than littermate controls and have reduced levels of cholesterol, adipokines, insulin, and fasting glucose.[23,24] Reduced adiposity of these transgenic mice appears to be due to systemic weight regulation that results in decreased whole-body energy requirements, evidenced by the decreased food intake observed in these animals.[23] Although another study did not observe an anti-obesity effect of SIRT1 overexpression in transgenic mice fed a high-fat diet, these mice were protected against some metabolic effects of this diet. Benefits of SIRT1 overexpression included less inflammation, better glucose tolerance, and almost complete protection against hepatic steatosis.[25]

SIRT1 expression has strong links to insulin sensitivity. Reports indicate that SIRT1 is down-regulated in highly insulin resistant cells, while inducing its expression in these cells increases insulin sensitivity.[23] In skeletal muscle, SIRT1 contributes to the improvement of insulin sensitivity through the transcriptional repression of the protein tyrosine phosphatase 1B (PTP1B) gene.[26] In adipocytes, SIRT1 regulates insulin-stimulated glucose uptake and GLUT4 translocation, with greater SIRT1 activity attenuating insulin resistance.[16] In various rodent models of insulin resistance and diabetes, SIRT1 transgenic mice display improved glucose tolerance and insulin sensitivity, due in part to decreased hepatic glucose production and increased hepatic insulin sensitivity.[23] SIRT1 expression appears to improve pancreatic beta-cell function. In beta-cell lines in which SIRT1 expression is inhibited, insulin secretion is blunted. Conversely, increased expression of SIRT1 promotes improved insulin secretion.[27] These *in vitro* responses mirror what has been observed *in vivo*. In transgenic mice, bred to overexpress SIRT1 in pancreatic beta-cells, there is enhanced glucose-stimulated insulin secretion and improved glucose tolerance. This improvement of beta-cell function persists through the aging process and when these mice are fed high-fat diets.[28,29] SIRT1 also regulates cholesterol metabolism by deacetylating and activating LXRalpha, a nuclear receptor involved in cholesterol and lipid homeostasis.[30]

Less research has been conducted on the other members of the sirtuin family in conditions associated with obesity. The limited evidence suggests that SIRT2 is the most abundant sirtuin in adipocytes, where it appears to be involved in adipogenesis – adipocyte formation. Over expression of SIRT2 inhibits preadipocyte differentiation into adipocytes, while decreased SIRT2 expression promotes adipogenesis.[31] SIRT3 appears to influence both ATP formation (fatty acid oxidation) and adaptive thermogenesis. In mice lacking SIRT3, fatty acid oxidation disorders emerge during fasting, including reduced ATP levels. These mice also demonstrate a generalized intolerance to cold exposure during fasting, suggesting a disordered thermogenic response from brown adipose.[32,33] SIRT4 is expressed in beta-cells in the islets of Langerhans and is thought to play a role in mitochondrial regulation of insulin secretion.[34] SIRT6 influences the expression of a variety of glycolytic genes, including genes involved in glucose uptake, glycolysis, and mitochondrial respiration. It appears to be a critical element of glucose homeostasis, with SIRT6-deficient mice developing a lethal hypoglycemia early in life.[35] SIRT6 might also play a role in the mouse response to a high-fat diet. Transgenic mice bred to overexpress SIRT6 accumulate significantly less visceral fat and have much lower LDL-cholesterol and triglyceride levels when fed a high-fat diet compared to controls. They also display enhanced glucose tolerance and improved glucose-stimulated insulin secretion.[36]

In humans, available information on sirtuin interaction with weight has come from observational or calorie restriction studies. In a study of SIRT1 mRNA expression in lean and obese women, lean women were reported to have more than two-fold higher SIRT1 expression in subcutaneous adipose tissue compared to obese women.[37] In another study, adipose tissue SIRT1 mRNA expression had a positive association with energy expenditure and insulin sensitivity in 247 nondiabetic offspring of type 2 diabetic patients.[38] In a third study, SIRT1-SIRT7 gene and protein expression were determined in peripheral blood mononuclear cells from 54 subjects (41 with normal glucose tolerance and 13 with metabolic syndrome). Insulin resistance and metabolic syndrome were associated with low SIRT1 protein expression.[39] In these studies, SIRT1 expression has a negative association with obesity or issues related to obesity; however, whether increased SIRT1 is involved in protecting against obesity, is a marker for obesity resistance, or is altered in response to ongoing dietary, lifestyle, or environmental factors, has not been established and cannot be determined from the existing evidence.

What human evidence does make clear is that, similar to other species including other mammals, human sirtuin expression is sensitive to changes in calorie intake. SIRT1 mRNA was measured in adipose tissue biopsies from nine human volunteers before and after six days of total fasting. Levels in subcutaneous adipose tissue increased more than two-fold with fasting.[37] In another study, muscle biopsies were obtained at baseline and on day 21 from 11 nonobese men and women who underwent three weeks of alternate day fasting; a statistically significant increase in muscle SIRT1 mRNA expression was observed.[40] In a third study, diet-induced changes in adipose tissue gene expression were assessed in two sets of 47 obese women who were placed on either a low-fat (high-carbohydrate) or a moderate-fat (low-carbohydrate) hypoenergetic diet for 10 weeks. One thousand genes, including sirtuin genes, were

regulated by energy restriction. SIRT3 gene expression appeared to be sensitive to the fat-to-carbohydrate ratio of a restricted calorie diet, with increased expression during the moderate-fat diet.[41]

Resveratrol has been shown to have *in vitro* and *in vivo* effects on sirtuins that are suggestive of a potential anti-obesity effect. One of these is an ability to counteract circumstances, including high glucose or long-chain fatty acid concentrations, that otherwise reduce the expression of SIRT1.[39] Resveratrol also inhibits preadipocyte proliferation and differentiation;[42] decreases lipid accumulation in, and nonesterified fatty acid release from, adipocytes;[43] attenuates fat deposition in hepatic cells;[44] promotes differentiation of mesenchymal stem cells into osteoblasts at the expense of adipocyte formation;[45] enhances the lipolytic effect of epinephrine in adipose tissue;[37] stimulates glucose uptake by skeletal muscle cells;[46] enhances insulin sensitivity;[26] and protects isolated pancreatic islet cells against cytokine-induced cytotoxicity, which allows these cells to maintain normal insulin-secreting responses to glucose.[47] As previously mentioned, feeding mice resveratrol appears to counter some of the effects of a high-fat diet; protecting against insulin resistance, hyperglycemia, and dyslipidemia.[9] Another mice study reported similar benefits when resveratrol was added to a high-fat diet for 13 weeks. In addition to improving insulin sensitivity and glucose tolerance, resveratrol-fed mice had increased metabolic rate, better physical endurance, and reduced fat mass. Although the study did not attempt to monitor changes in sirtuins, resveratrol did change the activity of other proteins, some of which are known to be deacetylated by the sirtuin system.[48]

Fatty Liver Disease

The sirtuin system has a variety of links to alcoholic and nonalcoholic hepatic steatosis. In general, SIRT1 expression has a negative association with fatty infiltration of the liver in both rodents and humans. In rodents, these associations exist for nonalcoholic and alcoholic hepatic steatosis and appear to be related to inflammation and sirtuin interactions with liver fatty acid oxidation and transport.[49] Sirtuin-steatosis interactions appear to be mediated, at least in part, by sirtuin deacetylation of other proteins, which subsequently modulates the activity of these proteins and their metabolic targets. For example, in a cell model of hepatic fatty infiltration, SIRT1 protects against hepatic fat deposition via induction of FOXO1 expression and repression of SREBP1 expression.[44] It has also been proposed that sirtuin effects on the PPARalpha/PGC-1alpha signaling axis might be involved in the protective association.[49]

In rodents, a high-fat diet plays a significant role in interactions with SIRT1 and nonalcoholic hepatic steatosis. Reduced expression of hepatic SIRT1 proteins appears to predispose mice to high-fat diet induced hepatic steatosis, while increased expression appears to protect against steatosis; this has been demonstrated in several studies. When mice, bred to have reduced expression of hepatic SIRT1, were fed a low-fat diet (5% fat), they were no more likely to have manifestations of fatty liver disease than normal mice. However, as dietary fat levels were increased in the mice with reduced hepatic SIRT1 expression, there was a corresponding increase in hepatic steatosis, with higher levels of dietary fat intake causing worse steatosis. These mice, in addition to significant increase in hepatic steatosis, experienced increased liver inflammation and hepatic lipogenesis, with a reduction in fat export.[50]

As mentioned in Part 1 of this review, sirtuins are both a regulating and a regulated protein. Deleted in breast cancer-1 (DBC1) is one protein with an established ability to regulate SIRT1. Mice bred to have a genetic deletion of DBC1 express increased SIRT1 activity in several tissues, including the liver. When these mice are fed a high-fat diet, they become obese but do not develop the hepatic steatosis and inflammation typically caused by this diet and that generally accompanies diet-induced obesity.[51] While increased SIRT1 expression appears to have a protective role against diet-induced hepatic steatosis, evidence also suggests that a high-fat diet can reduce SIRT1 expression. This suggests that an inability to counter the high-fat diet-induced downregulation of SIRT1 might play a role in susceptibility to diet-induced hepatic steatosis.[52]

SIRT1 expression might also play a role in fatty liver caused by other factors. Monosodium glutamate (MSG) is used to induce obesity and insulin resistance in mice and also results in increased hepatic steatosis. Coadministration of a pharmacological activator of SIRT1 with MSG administration from ages 6-16 weeks protects against hepatic steatosis in MSG-treated mice, despite having no protective effect on weight gain.[53]

Resveratrol appears to have a protective effect against hepatic fat infiltration. Wang et al also reported an ability of resveratrol to attenuate fat deposition in hepatic cells, secondary to inhibition of SREBP1 expression.[44] Hou et al observed a resveratrol-induced increase in SIRT1 deacetylase activity. They also detected effects on AMPK and several of its downstream targets, including acetyl-CoA carboxylase and fatty acid synthase. The net result of resveratrol treatment was prevention of hepatic lipid production – effects that were largely abolished by pharmacological and genetic inhibition of SIRT1 deacetylase activity. These findings suggests that resveratrol protects against fatty infiltration by activating SIRT1, which subsequently influences activity of other proteins and a variety of processes involved in the hepatic regulation of lipids.[54]

There are conflicting reports on the effects alcohol has on hepatic SIRT1. Chronic alcohol administration has been variously reported to decrease[55,56] and increase SIRT1.[57] The reason for this conflict is not completely clear, although it might be secondary to diet or other factors that influence SIRT1 expression. For example, Lieber et al reported that alcohol reduced hepatic SIRT1 when the fat in the diet consisted of long-chain triglycerides (LCT); however, replacement of LCT with medium chain triglycerides (MCT) restored hepatic SIRT1 almost to levels found without alcohol.[56] You et al reported that a high saturated-fat diet (40% of energy from cocoa butter) protected against the development of alcoholic fatty liver in mice, while a high polyunsaturated-fat diet (40% of energy from corn oil) did not. The protective effect appeared to be related to sirtuins because, compared with control mice, a diet high in saturated fat upregulated SIRT1 expression and suppressed the ethanol-induced increase in SREBP1, while the corn oil diet did not.[58] Despite the inconsistent response, available rodent research suggests that normalizing SIRT1 – increasing it when reduced by alcohol and decreasing it when increased by alcohol – might improve resistance to alcohol-induced fatty liver. This has been demonstrated with resveratrol administration.

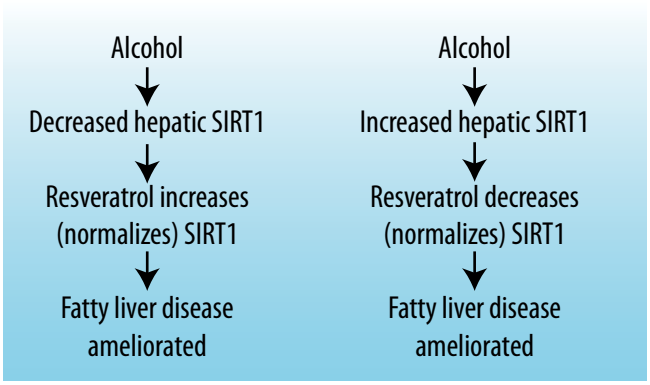
Amjo et al reported that SIRT1 activity was inhibited by ethanol. Resveratrol treatment increased SIRT1 expression in the liver of ethanol-fed mice. This increase was associated with suppression of SREBP1 and activation of PGC-1alpha. Resveratrol also reduced lipid synthesis, increased rates of fatty acid oxidation, and prevented alcoholic liver steatosis.[55] You et al reported that chronic ethanol feeding downregulated hepatic SIRT1 in mice. The reduced expression of SIRT1, since it was unavailable to deacetylate SREBP1, caused an upregulation of this protein. Treatment with resveratrol countered alcohol-induced effects on these regulatory proteins and protected against alcohol-induced fatty liver.[59] Oliva et al reported an opposite SIRT1 response to alcohol, but still observed a normalizing effect of resveratrol. One month of intragastric feeding of alcohol increased SIRT1 and led to steatosis. Treating alcohol-fed rats with resveratrol inhibited hepatic increase in SIRT1 and, while it was unable to prevent alcohol-induced macrovesicular steatosis, it did protect against necrosis and fibrosis. Hepatic SIRT3 expression was also upregulated by ethanol; resveratrol countered this increase.[57] These studies implicate sirtuins in alcohol-induced fatty liver disease, and suggest that resveratrol has the potential to help normalize hepatic SIRT1 and other proteins and protect against alcohol-induced fatty liver.

While studies report a mixed response of hepatic SIRT1 to alcohol, resveratrol administration appears to exert an adaptogenic effect by normalizing this response whether alcohol induced an increase or decrease of hepatic SIRT1.

Evidence of interactions with other members of the sirtuin family and fatty liver is sparse. *In vitro*, the number of lipid droplets in human hepatic cells overexpressing SIRT3 was significantly lower than that in control cells. Decreasing SIRT3 expression promoted lipid accumulation in these cells.[60] Under *in vivo* fasting conditions, SIRT3 expression prevents the accumulation of lipid droplets in hepatic cells.[32,60,61] Chronic alcohol-feeding also reduced SIRT5.[56]

In humans, SIRT1 expression in visceral adipose tissue was associated with severity of hepatic steatosis. In this study, morbidly obese individuals were divided into two groups – one with moderate hepatic steatosis and the other with severe steatosis. When comparing the two groups, a decrease of SIRT1 mRNA in visceral adipose tissue was detected in samples taken from the group with severe hepatic steatosis. Statistical analysis also revealed a positive correlation between mRNA expression of SIRT1 and homeostasis model assessment for insulin resistance (HOMA-IR).[62] The researchers did not explore whether the downregulation of SIRT1 mRNA expression in

Figure 2. Alcohol, Sirtuins, Resveratrol, and Fatty Liver



While studies have reported mixed response of hepatic SIRT1 to alcohol, resveratrol administration appears to normalize this response, whether alcohol leads to an increase or decrease of hepatic SIRT1. This suggests adaptogenic activity of resveratrol.

visceral adipose tissue was promoting steatosis in these obese individuals or a response to severe steatosis.

Cardiovascular System

In vitro and *in vivo* evidence suggests a role for several of the sirtuins in the cardiovascular system. SIRT1 appears to play a regulatory role in endothelial function. It is highly expressed in the vasculature, especially during periods of active blood vessel growth and vascular remodeling, when it appears to be involved in angiogenic activity of endothelial cells.[63,64] SIRT1 promotes endothelium-dependent vasodilation and regenerative functions in endothelial and smooth muscle cells of the vascular wall by targeting endothelial nitric oxide synthase for deacetylation, which stimulates the activity of this enzyme and increases endothelial nitric oxide production. If SIRT1 deacetylation is inhibited in endothelial tissue, nitric oxide synthase acetylation predominates, nitric oxide production decreases, and vasodilation is impaired.[65] SIRT1 might also play a significant role on endothelial function when blood sugar is elevated. Treatment of human endothelial cells with glucose decreases SIRT1 expression, induces endothelial dysfunction, and accelerates endothelial senescence. Increasing SIRT1 activity inhibits this glucose-induced endothelial senescence and dysfunction. These effects were also seen *in vivo*; activation of SIRT1 prevented hyperglycemia-induced vascular cell senescence and protected against vascular dysfunction in diabetic mice.[66]

In vitro research suggests resveratrol might augment endothelial SIRT1 expression under circumstances characterized by increased oxidative stress. Exposure of endothelial cells to cigarette smoke extract or hydrogen peroxide decreases SIRT1 levels and enzyme activity with a concomitant increase in acetylated (inactive) nitric oxide synthase. Pretreatment of endothelial cells with resveratrol attenuated the decline in SIRT1 levels and activity and resulted in less acetylation of nitric oxide synthase.[67] Other research reports resveratrol's endothelial vasoprotective effects[68] and its decrease in expression of angiotensin II type I receptor in vascular smooth muscle cells *in vivo*. This effect on angiotensin II type I receptors, apparently due to resveratrol's ability to increase expression of SIRT1, blunted angiotensin II-induced hypertension.[69]

SIRT1 might play a role in countering atherosclerosis due to its reported regulation of tissue metalloproteinase 3 (TIMP3). TIMP3 is an endogenous enzyme that counters vascular inflammation and is involved in the prevention of atherosclerosis. SIRT1 activity is also reportedly decreased in atherosclerotic plaques of subjects with type 2 diabetes – a decrease associated with reduced TIMP3 expression.[70]

SIRT1, SIRT3, and SIRT7 are expressed in cardiomyocytes, are upregulated during stress conditions (presumably as an adaptation to counter the stress), and appear to play a critical role in promoting cardiomyocyte resistance to stress and toxicity.[71-73] Cardiomyocyte protection appears to occur because of sirtuin deacetylation of other proteins, with the relative balance between acetylation and deacetylation of these targeted proteins influencing whether cardiomyocytes survive under stressful conditions.[72] Sirtuins also protect cardiomyocytes by activating antioxidant-encoding genes (including manganese superoxide dismutase and catalase) that decrease cellular levels of reactive oxygen species.[74]

Circumstances that result in decreased cardiac SIRT1 are associated with reduced cardiac function. For example, in mice with chronic type 1 diabetes, the enzymatic activity of cardiac SIRT1 is reduced, which contributes to reduced cardiac function and diabetic cardiomyopathy. Resveratrol increases SIRT1 activity and improves cardiac function in these mice.[75] *In vitro*, resveratrol increases SIRT1 and protects rat cardiomyocytes against hypoxia; pharmacological inhibition of SIRT1 reverses this protection.[76]

Doxorubicin is cardiotoxic, in part because it induces a rapid increase in reactive oxygen species. Pretreatment of cardiomyocytes with resveratrol inhibits the increase in oxidative stress caused by doxorubicin and prevents doxorubicin-induced cardiomyocyte death. These protective effects of resveratrol appear to be sirtuin-mediated, since they are abolished by nicotinamide, an *in vitro* sirtuin inhibitor.[77]

Streptozotocin injections in mice fed a standard-chow diet cause progressive decline in cardiac function associated with markedly reduced cardiomyocyte SIRT1 levels. Adding resveratrol to the diet of these mice increased SIRT1 activity in cardiomyocytes and improved cardiac function.[75]

In rats fed white wine, red wine, resveratrol, hydroxytyrosol, and tyrosol, heart expression of SIRT1 increased to the highest degree with white wine, followed by resveratrol, then tyrosol, hydroxytyrosol, and finally red wine. This was in contrast to the capacity of these dietary additions to offer cardioprotection (gauged by reduction of infarct size and cardiomyocyte apoptosis). Resveratrol provided the most protection, followed in descending order by red wine, hydroxytyrosol, white wine, and tyrosol.[78]

In vitro, nuclear but not cytoplasmic SIRT1 induced the antioxidant enzyme manganese superoxide dismutase, which was further enhanced by resveratrol. Resveratrol's enhancement of enzyme levels suppressed cell death induced by antimycin A or angiotensin II and was dependent on the level of nuclear SIRT1. Oral administration of resveratrol to hamsters also increased manganese superoxide dismutase levels in cardiomyocytes, which then suppressed fibrosis, preserved cardiac function, and significantly improved survival.[73]

Evidence suggests that resveratrol might help protect against myosin-induced autoimmune myocarditis of rats (a model of human dilated cardiomyopathy). Myosin-immunized rats experience an increase in SIRT1 in the myocardium and in infiltrating mononuclear cells compared with unimmunized rats. Despite the upregulation in SIRT1, myosin-immunization resulted in an increase in heart weight, fibrosis, and the expression of inflammatory cytokines. Resveratrol preserved cardiac function in these rats and protected against cardiomyopathy by decreasing fibrosis and inflammation, while normalizing expression of oxidative stress genes.[79]

While increased cardiomyocyte SIRT1 expression and activity appear to be an adaptation to stress and toxicity, limited evidence suggests that extremes of increased expression might not be desirable. Transgenic mice bred to have 2.5- to 7.5-fold heart-specific SIRT1 overexpression were protected against oxidative stress. Age-dependent increases in cardiac hypertrophy, apoptosis/fibrosis, cardiac dysfunction, and expression of senescence markers were consequently attenuated. However, a 12.5-fold overexpression of heart-specific SIRT1 increased oxidative stress, apoptosis, and hypertrophy, and decreased cardiac function, stimulating the development of cardiomyopathy.[80] In this case, rather than being protective and conferring resistance to age-related problems, the highest levels of SIRT1 expression promoted pathology. This may be a result of higher SIRT1 consumption of cellular NAD^+ exceeding the supply or unbalancing acetylation/deacetylation activities. Whatever the mechanism, these results suggest that the cardioprotective effects of heart-specific SIRT1 expression might be biphasic, with too much expression resulting in diminishing returns (Figure 3).

The importance of other sirtuins for cardiac function is apparent in SIRT3-deficient mice. In these mice, basal levels of ATP in the heart, kidney, and liver are reduced by more than 50 percent, and mitochondrial protein acetylation is markedly elevated in these same tissues. These mice also show signs of cardiac hypertrophy and interstitial fibrosis at age eight weeks and develop severe cardiac hypertrophy in response to hypertrophic stimuli.[81] Conversely, transgenic mice that overexpress SIRT3 are protected from stimuli-induced cardiac hypertrophy.[74]

SIRT7 also appears to be critical for cardiac function. SIRT7-deficient mice have reduced mean and maximum lifespans. Their hearts are characterized by extensive fibrosis, diminished resistance to oxidative and genotoxic stress, and a high basal rate of apoptosis resulting in cardiac hypertrophy and inflammatory cardiomyopathy.[82]

Brain and Nervous System

Several sirtuins expressed in the mammalian brain appear to play very different roles and respond in dissimilar ways to stress and toxicity. For example, Pfister et al reported that SIRT1 protects neurons against apoptosis, while SIRT2, SIRT3, and SIRT6 induce apoptosis in otherwise healthy neurons. SIRT5 has a dual role. In neurons, where it is located in both the nucleus and cytoplasm, it exerts a protective effect; however, in a subset of neurons where it is located in the mitochondria, it promotes neuronal death.[83] While

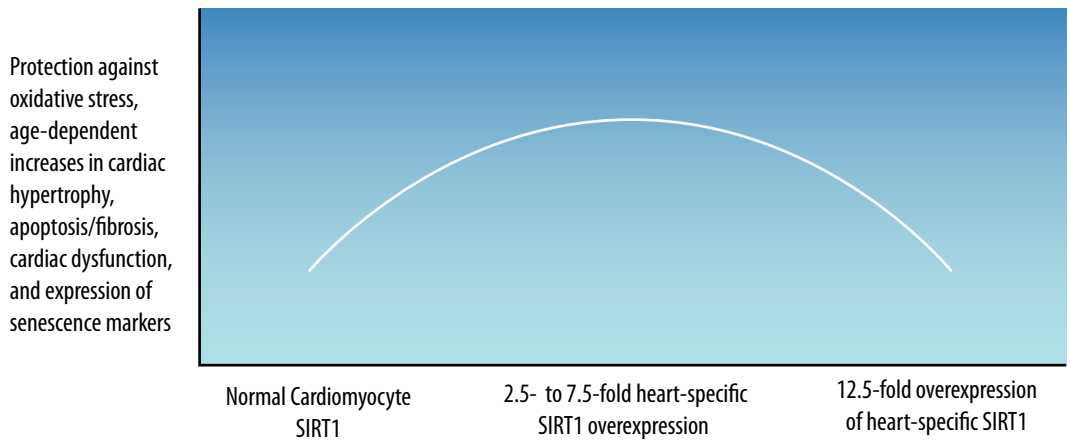
all these sirtuins appear to impact neurons, almost all research has focused on SIRT1 or SIRT2.

SIRT1 is ubiquitously present in areas of the brain that are especially susceptible to age-related neurodegenerative states (e.g., the prefrontal cortex, hippocampus, and basal ganglia). SIRT1 is also broadly distributed in the neurons that are most susceptible to senescence injury.[84] Calorie restriction results in upregulation of SIRT1 in some regions of the brain (such as the hypothalamus) and downregulation in others.[85,86] In mice undergoing calorie restriction, there is an attenuation of beta-amyloid content in the aging brain. This effect can be reproduced in mouse neurons *in vitro* by manipulating cellular SIRT1 expression/activity, suggesting it is a SIRT1-dependent process[87] and that SIRT1 upregulation might be protective under some types of nutritional stress. SIRT1 is upregulated in primary neurons challenged with some types of neurotoxic insults. However, in transgenic mice created to overexpress human SIRT1 in neurons, the neuronal overexpression of SIRT1 had no neuroprotective effects against damage induced by ischemia or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[88]

Evidence suggests that SIRT1 is upregulated in the brain in mouse models of Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS).[89] In cell-based models of these conditions, increased SIRT1 promotes neuronal survival.[89] In animal models of AD, cortical SIRT1 reduction parallels the accumulation of tau.[90] In humans with Alzheimer's disease, SIRT1 levels are also reportedly decreased in the parietal cortex but not in the cerebellum. Lower cortical SIRT1 was correlated with the duration of symptoms, lower global cognition scores, and accumulation of amyloid-beta and tau in the cerebral cortex.[90]

SIRT2, the most predominantly expressed sirtuin in the human brain,[91] is enriched in brain oligodendrocytes, where it is thought to be involved in differentiation, maturation, and remodeling.[92,93] SIRT2 is also highly expressed in post-mitotic neurons and glial cells.[94] In the brain and other tissues, SIRT2 acts as a tubulin deacetylase,[95-97] which inhibits growth in postmitotic neurons[97] and helps protect neuronal cells against mitotic stress.[98] SIRT2 is also highly expressed in the myelin sheath, where alpha-tubulin is its main protein target. Decreasing expression of SIRT2 in myelin increases alpha-tubulin acetylation and myelin basic protein expression; increasing expression of SIRT2 has the opposite effect.[99] Under some experimental circumstances SIRT2 inhibition appears to be neuroprotective.[100] Inhibition of SIRT2 activity also protects against dopaminergic cell death *in vitro* and in a Drosophila model of Parkinson's disease.[101] Under other circumstances it might be advantageous to express SIRT2. For example, SIRT2 is reportedly reduced in

Figure 3. Biphasic Effect of SIRT1 Overexpression



Evidence from transgenic mice bred to overexpress cardiomyocyte SIRT1 suggests a biphasic response when it comes to protecting the heart, with the best response occurring at a level of SIRT1 expression greater than normal but less than the highest levels of expression.

some human brain tumor cell lines, which apparently causes a relative loss of tumor suppressor activity via its role in protein deacetylation.[91]

Secondary to its role as a mediator of sirtuin activity, resveratrol appears to have a variety of brain and neuron effects. *In vitro*, by upregulating SIRT1, resveratrol protects neurons from apoptosis by excitotoxins (glutamate and NMDA).[102] Resveratrol improves neuronal cell survival in response to oxidative stress[103] and protects neuronal cells from ischemic insults.[104] Resveratrol pretreatment of mice is neuroprotective and induces tolerance against brain injury caused by cardiac arrest. These protective effects are associated with a resveratrol-induced increase in hippocampal SIRT1 activity.[105] Existing evidence suggests that resveratrol might counter some aspects of Alzheimer's disease. In cell-based models of AD, SIRT1 is increased and promotes neuronal survival; treatment with resveratrol also promotes survival. In the inducible p25 transgenic mouse, a model of AD and tauopathies, resveratrol reduced neurodegeneration in the hippocampus and prevented learning impairment. Resveratrol also decreased the acetylation of the SIRT1 protein substrates PGC-1alpha and p53, which suggests a supportive role on SIRT1 deacetylation.[89]

Resveratrol might be advantageous under some circumstances, but not in others. In cultured cerebellar granule cells taken from slow Wallerian degeneration mice (mice that have delayed axonal degeneration after injury), resveratrol diminished resistance to axonal degeneration. This appeared to occur because resveratrol enhanced neuronal SIRT2, which then promoted tubulin deacetylation that led to axonal degeneration.[106] It appears there might be circumstances where resveratrol would, secondary to its impact on the sirtuin system, result in unwanted responses in the brain nervous system.

Evidence suggests melatonin influences SIRT1. *In vitro*, it acts as a SIRT1 inducer in young and aged neurons[107] and increases SIRT1 and improves deacetylation in senescence-accelerated mice.[14] Limited evidence suggests it might also play a role during sleep deprivation. Rats subjected to total sleep deprivation for five days had reduced SIRT1 activity in hippocampal pyramidal and granular cell layers, which significantly impaired performance on behavioral memory tests. Supplying melatonin preserved SIRT1 activity and resulted in considerably better performance in the memory tests.[108]

As was discussed in detail in Part 1 of this review, nicotinamide is capable of sustaining sirtuin activity (by being recycled into NAD^+ via its salvage pathway) or inhibiting it, depending on the context. *In vitro* experiments indicate that supplying exogenous nicotinamide preserves NAD^+ levels, while preventing the excitotoxin-induced reduction in neuron SIRT1 activity.[86,102] Degeneration of an axon after it is severed can be significantly slowed in the presence of NAD^+ or its precursors – an effect that appears to be secondary to SIRT1 acitivitation.[109]

Because the nicotinamide salvage pathway in the brain is not as robust as in other tissues, the brain might be particularly susceptible to NAD^+ depletion under circumstances where its rate of use is increased. Supplying nicotinamide under these circumstances appears to regenerate NAD^+. Evidence suggests that exogenous nicotinamide might act as a sirtuin inhibitor in other circumstances. In AD transgenic mice, oral administration of nicotinamide restored cognitive deficits associated with AD by selectively reducing a specific phospho-species of tau (Thr231) that is associated with microtubule depolymerization, in a manner similar to inhibition of SIRT1. Nicotinamide also dramatically increased acetylated alpha-tubulin, a primary substrate of SIRT2 deacetylase.[110] In this study, nicotinamide appeared to inhibit SIRT1 and SIRT2 deacetylation reactions.

Cancer

The current understanding of the relationship between cancer and sirtuins was accurately stated in the title of a review article by Deng – "SIRT1, is it a tumor promoter or tumor suppressor?"[111] This title aptly captures the current confusion regarding cancer and sirtuins. Deng reports some evidence suggests SIRT1 is a tumor promoter, including increased SIRT1 expression in some cancers,[112-118] and its role in deacetylating (and hence presumably deactivating) proteins like p53, p300, and foxhead transcription factors that are involved in tumor suppression and DNA repair.[119-125] Conversely, other cancers have decreased expression of SIRT1.[117,126-128] Other indications of SIRT1 as a tumor suppressor come from experimental results of mouse/cancer models in which SIRT1 is intentionally under- (tumorigenesis increases) or overexpressed (tumorigenesis is attenuated).[117,126] SIRT1 also exerts a positive influence on other proteins and processes that result in suppression of tumor growth and enhanced DNA repair.[126,129-131] Consult the Deng article for an in-depth review.[111]

Like SIRT1, SIRT3 also appears to have both tumor promotion and tumor suppression effects. Although it is capable of deacetylating p53,[120] it is involved in supporting pro-apoptotic processes by targeting other proteins for deacetylation[32,132] and functions as a tumor suppressor by enhancing the expression of mitochondrial antioxidant enzymes.[133] Mice lacking SIRT3 express genomic instability and develop tumors.[133]

Conflicting evidence exists, even within the same cancer tissue type. Ashraf et al reported an association between increased SIRT3 and node-positive breast cancer,[134] while Kim et al reported reduced SIRT3 levels in breast (and other cancers) and noted that mice lacking SIRT3 develop mammary tumors.[133]

Although less is known about the other sirtuins and cancer, several have functions that suggest a role in cancer prevention. SIRT5 appears to regulate DNA repair and influences apoptosis.[135] SIRT6 is involved in regulating chromatin structure, maintaining telomere integrity and genomic stability, and repairing DNA.[136-141] SIRT7 promotes ribosomal gene (rDNA) transcription factors and has anti-proliferative effects.[142,143]

Sirtuin expression is thought to be a protective response to certain forms of stress and toxicity. Some cancer therapies, including radiation and certain forms of chemotherapy, are genotoxic. Limited experimental evidence suggests that the sirtuin system might respond to these treatments to protect cells against them, which might also potentially interfere with the clinical efficacy of these treatments. For example, exposure of cells to radiation caused an increase in SIRT1 and a corresponding increase in DNA repair. Experimentally-induced overexpression of SIRT1 resulted in a greater increase in repair of DNA strand breakages produced by the radiation. Conversely, inhibiting SIRT1 expression resulted in a decrease of DNA repair in response to radiation.[144] Other *in vitro* evidence reported inhibition of SIRT1 expression increased the efficacy of radiation against human lung cancer cells[145] and lack of SIRT1 increased cell sensitivity to radiation.[146] The relationship between SIRT1 and cisplatin has also been investigated *in vitro*. SIRT1 appears to be part of the cellular response to cisplatin, with greater SIRT1 expression associated with increased resistance of cancer cells to this treatment. Conversely, interfering with SIRT1 expression sensitized cells to cisplatin.[147] SIRT1- and SIRT2-deficient cells were also reportedly more sensitive to the pro-apoptotic effects of cisplatin and staurosporine.[146] This evidence, although *in vitro* and limited, suggests there might be interactions with the sirtuin response and certain cancer therapies that might interfere with or mitigate the efficacy of these therapies.

Resveratrol might have some sirtuin-mediated interactions with cancer. *In vitro* and *in vivo*, SIRT1 appears to be a potential interface between the tumor suppressor gene breast cancer 1 (BRCA1) and survivin (a negative regulator of apoptosis). Experimentally, BRCA1 binds to the SIRT1 gene and increases its expression; SIRT1 in turn inhibits survivin, resulting in programmed cell death. Absence of SIRT1 results in overexpression of survivin and impedes apoptosis. *In vitro*, resveratrol activates SIRT1, which then inhibits survivin expression and promotes apoptosis.[128] *In vitro*, resveratrol was also a potent sensitizer for cancer drug-induced apoptosis. One of the mechanisms of action for this effect is a downregulation of survivin expression.[148] While this study did not attempt to monitor SIRT1, it is possible that SIRT1 activation was involved in the downregulation of survivin, since SIRT1 is involved in regulating the expression of the survivin gene. *In vitro*, resveratrol dose-dependently induced apoptosis in osteosarcoma cells, but had a minor effect on normal osteoblasts. This difference in effect might be partly explained by SIRT1 expression, since SIRT1 is expressed in higher amounts in osteosarcoma cell lines than in normal human osteoblasts.[149] *In vitro*, resveratrol promotes autophagy (a mechanism that causes death of stressed cells by means other than apoptic or necrotic demise), apparently mediated by SIRT1 activation.[150,151] Resveratrol's activation of SIRT1 also promoted improved DNA repair activity subsequent to genotoxic stress.[152] Mice bred to underexpress SIRT1 and p53 develop tumors in multiple tissues, and administration of resveratrol reduced tumorigenesis in these mice.[127] Topical application of resveratrol has been reported to reduce tumorigenesis in a mouse model of skin cancer, an effect that was significantly reduced in mice lacking the SIRT1 gene.[153]

Conclusion

As research has better characterized the sirtuin system, it has become apparent that this system regulates many proteins, which themselves influence a variety of cellular processes. Because of their impact on the function of a diverse array of proteins, sirtuins are involved with metabolic responses and processes that influence many aspects of human function. Existing evidence

strongly supports sirtuin involvement in longevity, age-related diseases, obesity, cardiovascular and neurological function, and cancer.

As the responses become better understood, which sirtuins to target for activation or inhibition should become clearer. Cancer is a good example. Experimental evidence argues that sirtuins play a complex, more nuanced role in cancer than can be determined by its effects on any protein or metabolic process viewed in isolation. The complicated and perhaps competing effects of individual sirtuins on cellular processes that influence cancer development, suppression, and progression suggest much more research is required. Although SIRT1 has been found to increase in some cancers and not in others, its increase alone cannot be taken as evidence that it is a cause of cancer development. On the other hand, it could be a *consequence* of tumorigenesis or other factors involved in cancer or an adaptive response intended to counter genotoxic insults that contribute to cancer. Although sirtuin expression might counteract the desired clinical response to certain cancer therapies, specifically radiation and chemotherapy, there might be times when an increased sirtuin response might enhance cancer prevention or treatment. Currently there are as many questions as there are answers.

Resveratrol has generally been characterized as a sirtuin activator. It is possible that this might be an oversimplification of its actions. While it does appear to activate sirtuins under most circumstances, some evidence suggests a more adaptogenic effect on sirtuins. Available *in vitro* and *in vivo* evidence suggests that resveratrol is most likely to produce a noticeable physiological effect under stressful circumstances or those involving unhealthy lifestyle habits. For example, when mice were fed standard- and high-fat rat chow diets, the effects of resveratrol were significantly more dramatic in countering the effects of the latter diet. Presumably, this is because expression and activity of sirtuins are strongly influenced by environmental factors, especially dietary, lifestyle, or environment factors that create some form of stress. Although resveratrol might play a significant role in augmenting the sirtuin response, human research is required before any definitive inferences can be made.

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