

Skeletal muscle SIRT1 and the genetics of metabolic health: therapeutic activation by pharmaceuticals and exercise

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Abstract: Silent mating type information regulation 2 homolog 1 (SIRT1) is implicated in the control of skeletal muscle mitochondrial content and function through deacetylation of peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) and participation in the SIRT1/PGC-1 α axis. The SIRT1/PGC-1 α axis control of skeletal muscle mitochondrial biogenesis is an important therapeutic target for obesity and obesity-related metabolic dysfunction, as skeletal muscle mitochondrial dysfunction is implicated in the pathogenesis of multiple metabolic diseases. This review will establish the importance of the SIRT1/PGC-1 α axis in the control of skeletal muscle mitochondrial biogenesis, and explore possible pharmacological and physiological interventions designed to activate SIRT1 and the SIRT1/PGC-1 α axis in order to prevent and/or treat obesity and obesity-related metabolic disease. The current evidence supports a role for therapeutic activation of SIRT1 and the SIRT1/PGC-1 α axis by both pharmaceuticals and exercise in the treatment and prevention of metabolic disease. Future research should be directed toward the feasibility of pharmaceutical activation of SIRT1 in humans and refining exercise prescriptions for optimal SIRT1 activation.

Keywords: SIRT1, PGC-1 α , resveratrol, obesity, metabolic disease, exercise

Introduction

Decreases in mitochondrial content and function accompanying the development of overweight and obesity represent an underlying mechanism of several metabolic disorders including insulin resistance, dyslipidemia, type II diabetes, hypertension, and cardiovascular disease.^{1,2} In 2005, an estimated 23.2% of the worldwide adult population was overweight and 9.8% was obese.³ Current projections predict that 58.7% of the global adult population will be overweight or obese by 2030,⁴ an estimate that potentially represents a massive economic burden for healthcare systems worldwide. In the United States, these rates would increase obesity-related costs to 16% (USD860 billion) of total healthcare expenditure.⁴ Type II diabetes alone is already costing USD376 billion each year globally, a figure that is projected to grow 30% in the next 20 years.^{5,6} Given the economic and health costs associated with overweight and obesity, and their associated diseases, there is an urgent need for effective preventative and therapeutic interventions targeting weight gain and metabolic disease.

Skeletal muscle accounts for approximately 40% of body mass⁷ and plays a critical role in the maintenance of metabolic health. Healthy skeletal muscle has a highly oxidative phenotype, readily oxidizes lipids, is sensitive to insulin, and efficiently stores glucose.^{8,9} Consistent with the importance of mitochondria in healthy muscle, impairments in skeletal muscle function that contribute to obesity-related

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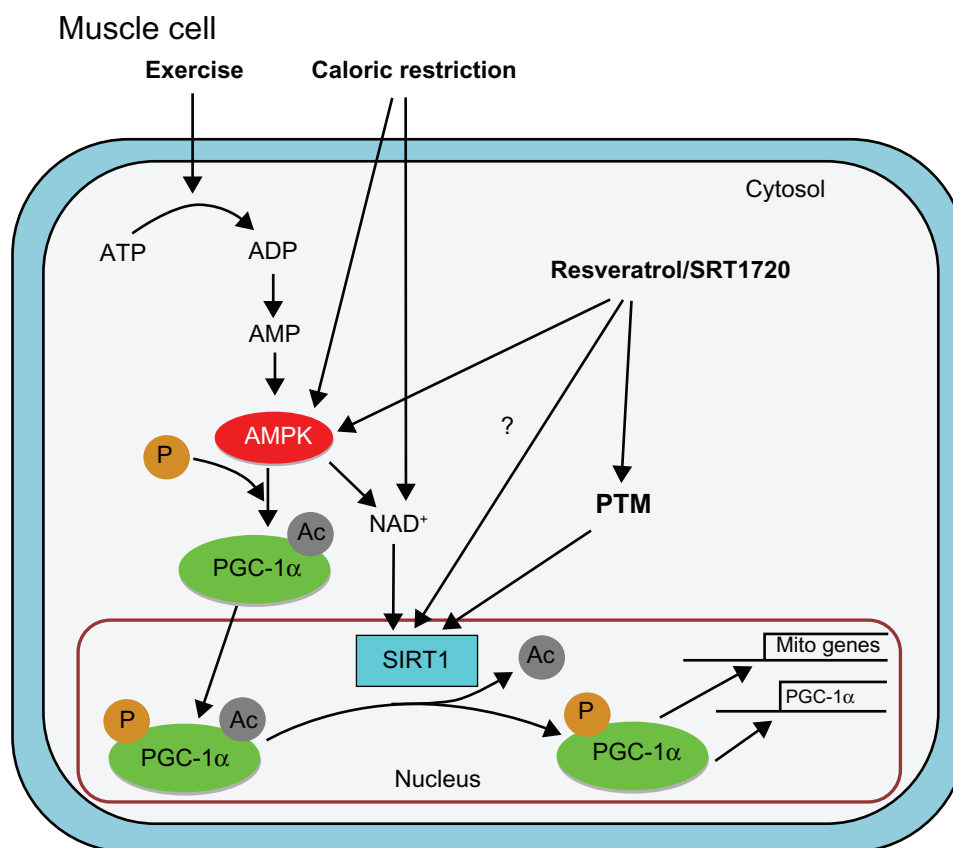


Figure 1 Model of pathways leading to activation of the silent mating type information regulation 2 homolog 1 (SIRT1)/peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) axis in skeletal muscle: SIRT1 deacetylase activity is directly influenced through posttranslational modification and indirectly through exercise, caloric restriction, and pharmaceutical activation.

Notes: Exercise-induced activation of adenosine monophosphate-activated protein kinase increases nicotinamide adenine dinucleotide, a necessary substrate in the SIRT1 deacetylase reaction, and directly phosphorylates cytosolic PGC-1 α prior to nuclear translocation. Caloric restriction activates adenosine monophosphate-activated protein kinase and increases nicotinamide adenine dinucleotide, while pharmaceuticals (resveratrol/SRT1720) activate adenosine monophosphate-activated protein kinase, induce SIRT1 posttranslational modification, and may augment SIRT1 deacetylase activity through direct interaction (dashed line). SIRT1 activates PGC-1 α through deacetylation, increasing PGC-1 α -mediated autoexpression and transcription of mitochondrial genes.

Abbreviations: Ac, acetyl; ADP, adenosine diphosphate; AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; NAD⁺, nicotinamide adenine dinucleotide; P, phosphate; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator-1 α ; PTM, posttranslational modification; SIRT1, silent mating type information regulation 2 homolog 1.

disease (eg, decreased fatty acid oxidation, impaired insulin sensitivity) are causally linked to decreases in mitochondrial content and function.^{10–15} In fact, decreases in mitochondrial content are apparent in early-stage overweight and obesity, and appear to contribute to both weight gain per se and to the metabolic dysfunction that underlies the development of metabolic disease.^{10,16}

Genetic control of skeletal muscle mitochondrial content is regulated via a complex network of signaling pathways, transcriptional factors, and transcription cofactors. Peroxisome proliferator-activated receptor γ coactivator 1- α (PGC-1 α) is a transcription factor coactivator that has been implicated as a key regulator of mitochondrial gene expression and mitochondrial biogenesis (Figure 1).¹⁷ The central role of PGC-1 α in the regulation of mitochondrial content has positioned this protein as an important target in therapies aimed at preventing

and/or treating disease.^{18,19} Silent mating type information regulation 2 homolog 1 (SIRT1) interacts with PGC-1 α in skeletal muscle increasing PGC-1 α 's transcriptional activity through deacetylation.²⁰ Given its apparent ability to activate PGC-1 α and increase mitochondrial content in skeletal muscle,²⁰ SIRT1 has itself been implicated as a key player in metabolic health.^{21,22} It should be noted that SIRT1 is not solely responsible for the control of PGC-1 α acetylation status, and evidence of normal mitochondrial biogenesis in mice lacking SIRT1 deacetylase activity suggests an inherent redundancy in the PGC-1 α deacetylation pathway.²³ Despite this redundancy, the bulk of evidence suggests an important role of SIRT1 in skeletal muscle adaptations; thus, there is considerable interest in interventions designed to target SIRT1 and the SIRT1/PGC-1 α axis as a means of increasing mitochondrial content, skeletal muscle function, and metabolic health.

Within this context, this review will first examine the role of skeletal muscle mitochondria in the development of obesity and metabolic disorders and the importance of the SIRT1/PGC-1 α axis in the determination of skeletal muscle mitochondrial content. Once the importance of the SIRT1/PGC-1 α axis to metabolic health has been established, potential interventions – pharmacological and otherwise – designed to activate SIRT1 in an attempt to prevent and/or treat obesity and obesity-related metabolic disorder will be examined.

Skeletal muscle mitochondria: mechanisms of metabolic disease

Although not all individuals who are overweight or obese develop metabolic disorders, in general, there appears to be a progression from overweight, to obese, to metabolically diseased. Consistent with this idea, being overweight as a young adult is highly predictive of obesity later in life,²⁴ and adult obesity is strongly associated with increased risk for many diseases, including insulin resistance, type II diabetes, and cardiovascular disease.^{1,2,11,25} Changes in mitochondrial content and function are implicated in the development of several metabolic diseases. While the importance of mitochondrial dysfunction is controversial,²⁶ there is significant evidence that mitochondrial content is altered in metabolic dysfunction. For example, the decline in skeletal muscle mitochondria associated with altered metabolic health is eloquently demonstrated by observations that mitochondrial oxidative capacity is lower in obese than in lean adults, and further decreased in type II diabetics (ie, lean > obese > type II diabetes).¹⁰ Further, a positive correlation has been observed between mitochondrial oxidative capacity and insulin sensitivity in lean and obese young adults^{27,28} and in sedentary and exercise-trained older adults.²⁹ While it is not clear whether mitochondrial dysfunction (defined as either decreases in individual mitochondrial oxidative capacity and/or decreased mitochondrial content) precedes initial weight gain, there is substantial evidence that mitochondrial function is impaired in both obesity^{11,28,30,31} and type II diabetes.^{14,32} At present, there is still debate regarding the exact mechanism(s) linking mitochondrial dysfunction to metabolic disease; however, the current literature suggests that either impaired fatty acid oxidation and/or increased oxidative stress resulting from altered mitochondrial function are central in the etiology of metabolic disease.

Fatty acid oxidative capacity is correlated with insulin sensitivity in obese individuals³⁰ and impairments in

lipid oxidation, accompanied by a concurrent upregulation of fatty acid transport,³⁰ appear to underlie the accumulations of intramuscular fat associated with obesity and metabolic disease.¹¹ Impaired lipid oxidation in obese skeletal muscle appears to be related to dysfunctional mitochondria lacking appropriate oxidative enzyme activity, decreased mitochondrial content within skeletal muscle, or a combination of both.^{10–12,16,26,33} As individuals progress from obesity to metabolic disease, there is a decrease in the content or quality of mitochondria, which results in an accumulation of intramuscular fat that is intimately related to decreases in metabolic health.

The accumulation of intramuscular fat is implicated in the development of a number of comorbidities, particularly insulin insensitivity and type II diabetes.^{8,34–37} Intramuscular lipid accumulation and the associated increases in lipid species, particularly diacylglycerol³⁸ and ceramides,^{35,39} have been linked to the disruption of the insulin receptor cascade.²⁶ Decreased insulin action (insulin insensitivity and the eventual development of insulin resistance and type II diabetes) is independently associated with the progression of hypertension and hyperlipidemia, and is known to be atherogenic.^{34,40}

In addition to a decreased capacity to oxidize fat, impaired mitochondrial function also contributes to chronic increases in oxidative stress via increased lipid peroxidation. Decreased fatty acid usage results in slowed intramuscular lipid turnover and a resulting maladaptive peroxidation of intramuscular lipids and reactive lipid species accumulation.^{41,42} Lowered lipid turnover rates, coupled with dysfunctional mitochondria prone to reactive oxygen species production, facilitate the peroxidation of lipids and the production of lipotoxic lipid species in the intramuscular lipid pool.⁴³ These lipotoxic lipid species further interfere with mitochondrial function and intracellular signaling through the disruption of protein and DNA structure, potentiating lipid peroxidation in a damaging cycle that contributes to the development of metabolic disease (see Schrauwen and Hesselink for a detailed review).⁴³

The importance of skeletal muscle mitochondria for overall metabolic health is illustrated through the association of mitochondrial dysfunction and metabolic disease. The accumulation of damaging reactive lipid species within the muscle is hypothesized to result from impaired mitochondrial function, and the ensuing oxidative stress is implicated in the pathophysiology of a host of metabolic diseases. Specifically, oxidative stress is suggested to contribute to the development of obesity and several other diseases associated with metabolic syndrome, including coronary artery disease, hypertension, and type II diabetes. For more detailed information on the

role of oxidative stress in obesity and metabolic disease, the reader is referred to Furukawa et al and Roberts and Sindhu.^{44,45} The activation of PGC-1 α has been implicated in the control of antioxidant expression and the prevention of mitochondrial oxidative damage in mice,⁴⁶ reinforcing the importance of targeting the SIRT1/PGC-1 α axis to improve metabolic health. Improving skeletal muscle mitochondrial content may reverse this lipid accumulation and potentially ameliorate the associated metabolic dysfunction. Thus, skeletal muscle mitochondrial content, through its role in the determination of intramuscular fat content, is intimately related to systemic metabolic health.

Genetic control of skeletal muscle mitochondrial content: the SIRT1/PGC-1 α axis

Plasticity is a defining characteristic of skeletal muscle; thus, there is great potential for the remodeling of metabolic function towards a healthy phenotype in all populations. For example, exercise training can significantly increase mitochondrial oxidative activity and fat oxidation, decrease intramuscular lipid accumulation and oxidative stress, and improve insulin sensitivity – all parameters of healthy skeletal muscle.^{36,47–49} These adaptations are largely due to increases in mitochondrial content and function resulting from the upregulation of a genetic program of mitochondrial protein controlled through the SIRT1/PGC-1 α axis.

PGC-1 α drives the transformation of skeletal muscle towards an oxidative phenotype via interaction with, and activation of, a plethora of transcription factors involved in the induction of mitochondrial genes encoded within both nuclear and mitochondrial DNA.^{17,18,50–52} While the regulation of the transcriptional activity of PGC-1 α is complex,^{53,54} induction of PGC-1 α -mediated transcription is accomplished through the acute activation of PGC-1 α ^{55,56} and chronic upregulation of PGC-1 α protein content via an autoregulatory loop.⁵⁷ Importantly, the acute activation of PGC-1 α , accomplished via posttranslational modification, appears to be an essential first step in the induction of PGC-1 α -mediated transcription of mitochondrial genes.²¹ PGC-1 α is posttranslationally modified by phosphorylation via p38 mitogen-activated protein kinase and adenosine monophosphate-activated protein kinase (AMPK).^{58–60} In addition, PGC-1 α acetylation status is also implicated in PGC-1 α transcriptional activity and mitochondrial biogenesis.^{20,61} For example, acetylation levels of PGC-1 α are inversely correlated with oxidative capacity in murine

skeletal muscle,⁶² while genetic mutation of acetylation sites on PGC-1 α (mimicking the deacetylated state) markedly increase PGC-1 α transcriptional activity and mitochondrial biogenesis in skeletal muscle cells.⁶²

Through the deacetylation of acetylated-lysine residues, the sirtuins (a family of evolutionarily conserved deacetylase) modify protein activity and have been implicated in a variety of cellular processes, including the stress response and cellular energy control in mammals.^{22,63,64} While seven sirtuins have been identified in humans, several of which are implicated in metabolic control, including the mitochondrial sirtuins SIRT3, SIRT4, and SIRT5,⁶⁵ the current review will focus on SIRT1 in skeletal muscle and metabolic disease. SIRT1 directly interacts with PGC-1 α in mouse hepatocytes,⁶¹ and is responsible for deacetylation of PGC-1 α in 293T cells⁶¹ and PC12 neuronal cells.⁶⁶ In addition, SIRT1 interacts with PGC-1 α in C2C12 skeletal muscle cells,²⁰ and SIRT1-mediated deacetylation of PGC-1 α appears to play an important, but perhaps nonessential,²³ role in the induction of PGC-1 α -mediated transcription.⁶² In support of this evidence from cells, SIRT1 is implicated in caloric restriction, exercise, and aminoimidazole carboxamide ribonucleotide-induced upregulation of mitochondrial content and function in skeletal muscle of mice.^{20,62,67} Further, in transgenic animal models, overexpression of SIRT1 consistently improves insulin sensitivity^{68,69} and exerts a protective effect against metabolic disorders commonly associated with high-fat feeding.⁷⁰ This evidence implicates the SIRT1/PGC-1 α axis in skeletal muscle in the upregulation of genes implicated in mitochondrial content,^{71,72} as well as fatty acid oxidation and energy expenditure,²⁰ and illustrates the importance of this axis for any intervention designed to reverse skeletal muscle dysfunction. As such, targeting the SIRT1/PGC-1 α axis may be a practical treatment model for obesity and metabolic disorder.

Physiological control of SIRT1 activity

In vivo, SIRT1 activity is regulated by substrate availability, posttranslational modification, and the formation of both inhibiting and activating complexes.⁷³ Activation of SIRT1 through one, or several, of these mechanisms is expected to upregulate mitochondrial gene expression via the SIRT1/PGC-1 α axis, resulting in improved mitochondrial and metabolic function.

Substrate availability is implicated in SIRT1 activation, primarily through changes in cellular redox potential. Nicotinamide adenine dinucleotide (NAD⁺) is a substrate

in SIRT1-mediated deacetylation, which suggests changes in NAD⁺ can affect SIRT1 activity.^{61,74} Consistent with this hypothesis, SIRT1 activity (measured as a decrease in PGC-1 α acetylation status) and NAD⁺ are increased concomitantly during nutrient deprivation in hepatocytes⁶¹ and C2C12 skeletal muscle cells,^{20,61} and following nutrient deprivation⁶⁷ and exercise^{62,67} in intact mouse muscle. Recent reports suggest that AMPK, an intracellular energy sensor,⁷⁵ mediates increases in NAD⁺ during periods of nutrient restriction, and thus plays a key role in regulating SIRT1 activity and transcriptional programs controlled through the SIRT1/PGC-1 α axis.^{62,67} Additionally, nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the NAD⁺ salvage pathway,^{76,77} is implicated in the control of intramuscular NAD⁺ and thus SIRT1 activity. NAMPT is upregulated following interventions known to activate SIRT1 in skeletal muscle – specifically, exercise training in humans⁷⁸ and acute exercise in mice.⁶⁷ These results comprise the main evidence supporting the hypothesis that SIRT1 activity is increased in response to altered energy status through increased substrate availability via AMPK, NAMPT, or both. Interestingly, in both cell and animal models,^{49,79–81} SIRT1 activity does not always correspond to changes in NAD⁺. These results suggest that SIRT1 activity is under more complex control than can be explained through alterations in substrate availability alone.

Several recent lines of evidence have implicated posttranslational modifications of SIRT1 and the formation of inhibitory^{82,83} and activating complexes in the control of SIRT1 deacetylase activity.^{84,85} A number of phosphorylation sites have been identified on SIRT1,^{86,87} and phosphorylation of these sites consistently increases SIRT1 deacetylase activity.^{86–88} In addition to phosphorylation, SIRT1 activity is influenced by sumoylation,⁸⁹ methylation,⁹⁰ and nitrosylation.⁹¹ Sumoylation by the small ubiquitin-like modifier family of enzymes increases SIRT1 catalytic activity,⁸⁹ while it is unclear whether methylation directly affects SIRT1 deacetylase activity.⁹⁰ Transnitrosylation of SIRT1 has also been demonstrated, resulting in increased acetylation of SIRT1 targets, suggesting an inhibitory effect on SIRT1 deacetylase activity with nitrosylation.⁹¹ In addition to posttranslational modifications, SIRT1 deacetylase activity can be modified through the formation of regulatory complexes. Specifically, SIRT1 deacetylase activity is inhibited when forming a complex with deleted in breast cancer-1⁸⁵ and activated when forming a complex with active regulator of SIRT1.⁸⁴ These types of SIRT1

activity regulations (both posttranslational modifications and regulatory complex formation) have not been thoroughly explored in skeletal muscle, making it an important direction for future research.

The physiological pathways controlling SIRT1 activity, outlined above, can be activated by both exercise and caloric restriction. The exact mechanism by which caloric restriction impacts SIRT1 activity remains unclear, although it is hypothesized that caloric restriction initiates a disturbance to metabolic homeostasis, activating AMPK and subsequently increasing cellular NAD⁺, resulting in an increased activation of SIRT1.^{20,21,61,62,67} Caloric restriction may also increase SIRT1 activity through activation of NAMPT, increasing flux through the NAD⁺ salvage pathway.⁹² Despite the uncertainty surrounding the mechanism of caloric restriction-mediated SIRT1 activation, it is apparent that caloric restriction increases SIRT1 deacetylation activity and can play a role in the activation of the SIRT1/PGC-1 α axis, increasing fatty acid oxidation in skeletal muscle,⁶² and providing protective metabolic effects against an energy imbalance.⁹³ For a more detailed review on the role of SIRT1 in caloric restriction, the reader is referred to Canto and Auwerx.^{21,93}

Pharmacological activation of SIRT1

In addition to physiological activation, SIRT1 can also be pharmacologically activated through interactions with a number of natural and synthetic molecules. Resveratrol, a naturally occurring polyphenol found in grape skins, has been implicated in the activation of SIRT1.^{72,94–96} While resveratrol administration can increase SIRT1 activity by as much as eight-fold,⁹⁶ the exact mechanism of activation remains elusive. Although it was initially believed that resveratrol interacts with and activates SIRT1 directly, more recent investigations have demonstrated that this interaction may be an artifact of the fluorophore detection method,^{97,98} and in vivo resveratrol-mediated activation of SIRT1 appears to result from activation of upstream targets.^{72,99,100} The synthetic production of SIRT1 activators has also been successful; in particular, SRT1720 increases SIRT1 deacetylase activity more potently than resveratrol in both cell lines and within skeletal muscle of mice.^{94,96,101} However, as with resveratrol, whether SRT1720 activates SIRT1 directly or indirectly remains unclear.^{98,101} Despite the uncertainty surrounding the mechanism of these molecules and their interaction with SIRT1, their ability to increase SIRT1 deacetylase activity is well established. The potential for activation of the SIRT1/PGC-1 α axis through

pharmacological means makes SIRT1 an intriguing target for future therapeutic intervention.

Targeting SIRT1 activation as therapeutic intervention

The remainder of this review will explore the potential benefits and limitations of targeting SIRT1, through pharmacological and physiological interventions, for the purpose of activating the SIRT1/PGC-1 α axis to stimulate mitochondrial biogenesis and improve skeletal muscle function and metabolic health.

Health benefits associated with pharmaceutical activation of SIRT1

The pharmacological activation of SIRT1 exerts its therapeutic effects on skeletal muscle through the SIRT1/PGC-1 α axis. By increasing mitochondrial content and function through PGC-1 α -mediated transcription, improved skeletal muscle function may prevent or reverse obesity and metabolic disease. In skeletal muscle, resveratrol activates SIRT1 resulting in deacetylation of PGC-1 α and the induction of a genetic profile associated with improved mitochondrial function and fatty acid metabolism.⁷² As mentioned previously, while SIRT1 is required for resveratrol-mediated deacetylation of PGC-1 α in mouse embryonic fibroblasts,⁷² there is some debate regarding resveratrol's direct interaction with SIRT1,^{98,102} with some evidence suggesting that resveratrol's effects may occur via an AMPK-mediated mechanism.^{72,99,100} Regardless, AMPK and SIRT1 are believed to function in concert in skeletal muscle,⁶⁷ and this uncertainty only questions whether resveratrol acts directly on SIRT1, not whether resveratrol activates the SIRT1/PGC-1 α axis.

Consistent with the above, activation of the SIRT1/PGC-1 α axis following resveratrol treatment in mice increases mitochondrial and fatty acid gene expression and increases mitochondrial content in skeletal muscle.⁷² Accompanying these improvements in skeletal muscle function are improved insulin sensitivity in mouse models^{72,99,103} and a resistance to the deleterious effects of aging and a high-fat diet on metabolic health.^{72,103,104} At present, there are relatively few studies examining the metabolic impact of resveratrol in humans. However, a recent study in obese males indicates that 30 days of dietary resveratrol supplementation increased skeletal muscle SIRT1, PGC-1 α protein content, and intrinsic mitochondrial function and improved several markers of

cardiovascular and metabolic health.¹⁰⁵ Two other studies have also reported beneficial effects of dietary resveratrol in humans, including improved glucose tolerance in older adults¹⁰⁶ and a reduction of the oxidative and inflammatory response to a high-fat meal.¹⁰⁷ While these studies provide promising initial findings indicating that targeting SIRT1 via resveratrol supplementation may prove therapeutic for obesity and obesity-related disease, randomized controlled studies are still needed to confirm these beneficial effects in a larger population. In addition, there are little data regarding whether a prolonged intake of resveratrol has any negative implications either within skeletal muscle, within other organs (liver for example), or on overall metabolic health in humans.

The use of the synthetic SIRT1 activator SRT1720 has been proposed to selectively activate SIRT1 with greater potency, efficacy, and selectivity than resveratrol.^{94,96,101} The chronic administration of SRT1720 in mice decreases acetylation of PGC-1 α and a number of other SIRT1 targets⁹⁴ and increases oxidative capacity, lipid oxidation, insulin sensitivity, and provides a protective effect against diet-induced obesity.^{94,95,101} In addition to protective metabolic effects, mice on high-fat diets given SRT1720 ran twice the distance in endurance trials and improved muscle function in a variety of functional tests when compared to controls fed the same diet.⁹⁴ These skeletal muscle adaptations make SRT1720 an appealing molecule for therapeutic intervention. Similar to resveratrol, controversy exists regarding whether SRT1720 activates SIRT1 through direct interaction, or acts indirectly via activation of AMPK through alterations in cellular energy status.⁹⁸ Thus the metabolic adaptations attributed directly to SRT1720–SIRT1 interaction versus an AMPK-mediated SIRT1 activation are difficult to distinguish.⁹⁴ Phase I and II clinical trials examining the safety and metabolic benefits of a drug closely related to SRT1720 (ie, SRT2104) are currently underway and represent an important look into the ability of SRT1720/2104 to increase mitochondrial content in skeletal muscle and improve metabolic function in obesity and metabolic disease.

At present, interventions with both resveratrol and SRT1720 in mice and in preliminary human studies (resveratrol only) appear to activate the SIRT1/PGC-1 α axis, improve mitochondrial content in skeletal muscle, and improve metabolic health. These findings support the suggestion that these pharmaceuticals are promising potential agents for the prevention and treatment of obesity and its related diseases, and warrant further investigation.

Health benefits of the SIRT1/PGC-1 α axis activation during exercise

Exercise, as a component of lifestyle intervention, is an alternative to pharmacological interventions aimed at improving skeletal muscle mitochondrial function and metabolic health.¹⁰⁸ An emerging line of evidence suggests that exercise targets SIRT1, and the resulting activation of the SIRT1/PGC-1 α axis underlies many of the beneficial effects associated with exercise.^{109,110}

An acute bout of exercise in rat and mouse muscle increases SIRT1 activity¹⁰⁹ and deacetylation of PGC-1 α immediately, and for several hours following exercise.^{62,67} Exercise training is also implicated in the activation of SIRT1 in animal models, with both increases in SIRT1 activity^{49,80,81,111} and deacetylation of PGC-1 α ¹¹² observed following chronic contractile activity and treadmill running. Activation of SIRT1 was also observed in human skeletal muscle after 2 weeks and 6 weeks of exercise training.^{71,109} While skeletal muscle SIRT1 protein content is also elevated following acute exercise and exercise training in both rats^{113,114} and humans,^{115,116} the implications of elevated SIRT1 content in muscle remain unclear.¹¹⁷ It should also be noted that although PGC-1 α deacetylation was normal in mice expressing SIRT1 lacking deacetylase activity,²³ the majority of observations in intact animal and human skeletal muscle support the involvement of SIRT1 in mediating PGC-1 α acetylation status. Also consistent with the contention that SIRT1 and the SIRT1/PGC-1 α axis play a critical role in the control of skeletal muscle mitochondrial content are numerous animal studies reporting that increased SIRT1 activity is accompanied by increases in PGC-1 α transcriptional activity.^{80,81,113,114,118}

The activation of the SIRT/PGC-1 α axis by exercise is accompanied by increases in markers of oxidative capacity and mitochondrial content in animals^{71,80,81} and humans.^{71,116} Further, markers of improved fatty acid oxidation and insulin sensitivity are also found in animals and humans accompanying activation of the SIRT1/PGC-1 α axis by exercise.^{71,114,116} In addition to mitochondrial adaptations, activation of the SIRT1/PGC-1 α axis is linked to the attenuation of age-related decline in skeletal muscle health in exercised rodents^{49,111,113} via decreased oxidative stress and DNA damage, factors also implicated in the pathogenesis of many metabolic disorders associated with obesity.⁴⁴ Consistent with these observations, exercise training improves oxidative capacity and fatty acid oxidation in skeletal muscle from obese adults,^{13,119,120} improves insulin sensitivity in obesity and type II diabetes,^{121,122} and decreases

both risk factors for, and symptoms of, metabolic disease.^{123,124} In summary, exercise appears to activate the SIRT1/PGC-1 α axis and improve skeletal muscle mitochondrial function and metabolic health. These results highlight the preventative and therapeutic potential of exercise for obesity and obesity-related disease.

As an alternative treatment in obesity and metabolic disease, exercise has several inherent advantages over pharmaceutical intervention. First, the improved metabolic function associated with exercise comes at minimal financial cost, while a pharmaceutical intervention carries a substantial financial commitment from both the individual and healthcare provider.^{4,6} Second, in addition to improved skeletal muscle mitochondrial function and metabolic/cardiovascular health, regular exercise is associated with a myriad of beneficial effects ranging from the prevention and treatment of mental disorders¹²⁵ and cancer¹²⁶ to alleviating symptoms and improving quality of life in many chronic diseases.¹²⁷ Third, exercise is implicated in a systemic improvement of health with little to no risk of adverse side effects.^{108,128} Pharmaceuticals are often associated with undesirable side effects, and are inherently designed to be specific, eliminating the possibility of a systemic health improvement. Finally, there is evidence that exercise, as part of a lifestyle intervention, induces superior improvements compared to pharmaceutical intervention in subjects with metabolic disease.¹²¹ In light of these arguments, it makes both health and financial sense that exercise becomes a first-line tool in both the prevention and treatment of obesity and obesity-related disease.

Conclusion and future direction

The current review has focused on the contribution of SIRT1 to skeletal muscle function and metabolic health. Future studies should not only continue to investigate SIRT1 function, but should also focus on other members of the sirtuin family. The contribution of SIRT1 to overall metabolic health occurs, in part, through SIRT1's influence on PGC-1 α and skeletal muscle mitochondrial function. As skeletal muscle mitochondrial dysregulation is implicated in obesity and obesity-related metabolic disease, SIRT1 has become an attractive target for therapeutic intervention. The activation of SIRT1, and consequently the SIRT1/PGC-1 α axis, results in upregulation of mitochondrial genes and improved skeletal muscle mitochondrial content and function. SIRT1 activity can be modified by pharmaceuticals and exercise, providing an array of options to pursue for implementing a therapeutic intervention. A clear need for further investigation of the feasibility of pharmaceutical intervention in humans is

evident as, for the most part, human trials are in their infancy or are nonexistent. With exercise, exploration of the optimal dose and intensity will expand the possibility of tailored prescriptions targeting SIRT1 activity.

Disclosure

The authors report no conflicts of interest in this work.

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