Obesity Medicine 17 (2020) 100156

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Role of sirtuins in obesity

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ARTICLE INFO

Keywords:
Obesity
Sirtuins
Calorie restriction
Adipogenesis
SIRT1
PPAR-γ
NAD^+

ABSTRACT

Purpose: The present enumerates the intrinsic role of sirtuins in the treatment of obesity and related complications.

Key findings: Various approaches have been made to reduce the progression of obesity and its associated disorders as it threatens the public health globally. Sirtuins (silent information regulator) is a conserved mammalian (nicotinamide adenine nucleotide) NAD^+ dependent protein deacetylase considered as promising target for treating various diseases e.g., cancer and neurodegenerative disorder. It consist of seven types of sirtuins including SIRT1, SIRT2, SIRT3, SIRT4, SIRT4, SIRT5, SIRT6, SIRT7, out which SIRT1 sirtuins emerged out as putative molecule in the treatment of obesity and act as metabolic sensor of glucose and lipids in liver by using short carbon fragment viz. acetyl coenzyme A. It play key roles in regulation of gene expression, aging, insulin secretion, insulin sensitivity, mobilization of stored fat, formation of white adipose tissue and brown adipose tissue, mediate inflammatory responses in macrophage. Additionally, SIRT1 regulate adipokines expression, act as therapeutic target for type II diabetes mellitus, deacetylates histone proteins inhibit the factors required for maturation of cells.

Conclusion: Alteration in the above physiological processes result in the development of obesity and obesity related disorder, so SIRT1 is emerged out as therapeutic molecule for the prevention of obesity. This review demonstrates the use of sirtuins as a potent agent in the treatment of obesity and the current status focus on the therapeutic potential of sirtuins in prevention of excessive accumulation of fat in adipose tissue.

1. Introduction

Obesity is a complex disorder that is associated with grossly elevated level of fat store in adipose tissue and it is manifested by both genetic and environmental factors. As a disease, it is the core of many chronic illness viz. coronary heart disease, diabetes, arthritis, gastrointestinal disorder, asthma, hypertension and certain form of cancer. The major cause of obesity are high caloric intake, or lack of physical exercise, mental and endocrine disorder or genetically. However, it is prevented through a combination of social changes including diet and exercise (Sikaris K, 2004; Alberti KG and Zimmet PZ, 1998). The excessive deposition of fat mass in adipose tissue result in insulin resistance and activation of certain inflammatory mediators and oxidative stress, perpetuates systemic response. Several diseases occurs due to obesity and with regulation of oxidative stress (Xu H et al., 2003). Oxidative stress is the disturbance between the free radicals and antioxidant in body that detoxify the reactive intermediate or repair the cell and tissue damage that leads to the production of peroxidase and free radicals that causes damage to cell viz. membranes, protein and strand breaks in DNA (Table 1, Figs. 1 and 2).

The sirtuins are NAD^+ dependent protein deacetylating enzymes that plays a significant role in metabolism, stress responses, insulin secretion and sensitivity, regulation of inflammation, body metabolic homeostasis and aging processes (Guarente L, 2011; Finkel T, Deng CX, Mostoslavsky R, 2009). Data conducted over the years revealed that sirtuins consist of seven mammalian sirtuins, out of which SIRT1 is localized in nucleus but transfer to cytosol, SIRT2 localized in the cytoplasm and regulate gene transcription, SIRT 3, 4 and 5 are the mitochondrial proteins apart from this SIRT 6 and 7 are nuclear. Sirtuins are activated in response to inflammation, oxidative stress in cell and tissue and their activity can be altered directly by phosphorylation, acetylation and protein interactions and indirectly by altering the level of NAD^+. The SIRT1 is best sirtuin that mediates transcriptional responses. Although, SIRT1 level is decreased due to increase glycolytic activity whereas during exercise SIRT1 activity increases due to increase in mitochondrial oxidative metabolism by deacetylating histones and non-histones gene regulatory proteins.

Biological effect of sirtuins – Increased activity of SIRT1 leads to lower cholesterol, blood glucose and insulin levels and regulates vasodilation by targeting eNOS. Sirtuins deacetylate stimulates their

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https://doi.org/10.1016/j.obmed.2019.100156
Received 10 October 2019; Received in revised form 1 November 2019; Accepted 4 November 2019

Table 1
Various function mediated by class of Sirtuins.

S.No.	Classes	Location	Function
1.	SIRT1	Nucleus	Glucose metabolism, differentiation, insulin secretion
2.	SIRT2	Cytosol	Cell –cycle control, lipid synthesis
3.	SIRT3	Mitochondria	Fatty acid oxidation, ATP-production
4.	SIRT4	Mitochondria	Insulin secretion, metabolism
5.	SIRT5	Mitochondria	Urea cycle, metabolism
6.	SIRT6	Nucleus	DNA repair, chromosomes stability
7.	SIRT7	Nucleus	RNA pol I transcription, ER stress

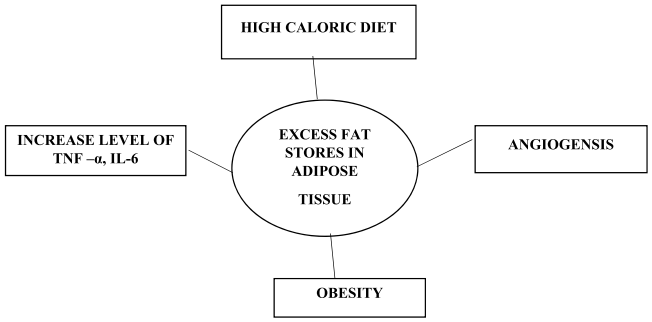

Fig. 1. Pathogenies of obesity.

activities either by changing the expression level, altering their binding to DNA. However the enzymatic activity of SIRT1 is very low in obesity due to alteration in the physiological processes which in turn leads to development of various metabolic related disorder associated with obesity (Revollo J R and Li X, 2013; Lee J and Kemper JK, 2010). Although it has been stated that the activity of SIRT1 is enhanced by natural SIRT1 activator (Hubbard BP et al., 2013) which in turn increase the cellular level of NAD^+ (Yoshino J et al., 2011; Cantó C et al., 2012).

SIRT 3 deacetylates is the another sirtuin present in the mitochondria that regulates activity of proteins present in mitochondria such as fatty acid oxidation, urea cycle and mediate oxidative stress response (He W et al.,. 2012; Hirschey MD et al., 2010; Qiu X et al., 2010) and it is hyper acetylated in obese patients in which SIRT1 activity is low, so SIRT3 inhibit its deacetylase activity of SIRT1 deacetylates and promote protein degradation.

1.1. Metabolic disorders linked with obesity and SIRT1

SIRT1 is the best studied sirtuins that inhibit the activity of peroxisome proliferator activated receptor gamma (PPAR-γ) (Picard F et al., 2004) regulate the expression of adiponectin, mitochondrial activity (Li Qiang et al., 2007; Qiao L and Shao J, 2006; Nemoto et al., 2005) and secretion of insulin (Bordone et al., 2007)and promote insulin sensitivity (Ramsey et al., 2008). However, all of the above listed parameters are deregulated in obesity. Data conducted over the years revealed that restriction of nutrients in turn leads to upregulation of SIRT1 and detects changes in NAD^+ levels and act by deacetylating forkhead box protein (FOXO), peroxisome proliferator activated receptor gamma coactivator1-alpha (PGC-1α), PPARγ and Nuclear factor kappa b (NF-κB). Although storage of fat in adipose tissue, high calorie intake leads to dysfunction of physiological responses that result in obesity.

Chromatin is complex structure made up of DNA wrapped around histones (Kornberg RD and Lorch, 1999) and it can be remolded into various patterns of gene expression via epigenetic mechanisms and leads to distinct patterns of gene expression, and the gene expression is regulated by SIRT1 (Longo VD and Kennedy BK, 2006; Pruitt K et al., 2006). Acetylation is a reversible post-translational modification mediated by histone acetyltransferases (HATs) and enzymes that reverse this modification is histone deacetylases III HDACs called as Silent Information Regulators (or sirtuins) and they require NAD^+ as a co-factor/substrate which leads to deacetylation of lysine and the product obtained is deacetylated lysine.

As we know SIRT1 promotes adipogenic program and regulates insulin sensitivity it also regulate cell survival in different organisms. For example, in an experimental study of diabetic nephropathy it was shown that SIRT1 was decreased in the diabetic rat kidney (Tikoo K et al., 2007). Although it was concluded that intermittent fasting, prevent the development of diabetic nephropathy, result in an increase in the expression of SIRT1. It has been stated that SIRT1 regulate cardiomyocyte contractile function in diabetic mouse model and fidarestat improves cardiomyocyte contractile function which is depend on the SIRT1 function (Dong F and Ren J, 2007).

1.2. Calorie restriction and SIRT1

Calorie restriction (CR) reduce age-related chronic diseases and extend lifespan in organisms by maintaining proper nutrition (Anastasiou D and Krek W, 2006; McCay CM et al., 1989; Michan S and Sinclair D, 2007). Various studies demonstrated a correlation between CR and SIRT1 by protruding that SIRT1 inhibitors (nicotinamide) and activators extend lifespan of yeast lifespan due to caloric restriction (Anderson RM et al., 2003).In an experiment done by Cohen et al. on rats when rats were subjected to intermittent fasting in turn leads to increased levels of SIRT1 and it also inhibit stress-induced apoptotic cell death by deacetylate the DNA repair factor Ku70. Therefore SIRT1 cause cells to remain viable under CR until the stress has been eradicated. Another study conducted by Nisoli et al. concluded that induction of eNOS stimulates mitochondrial biogenesis by increasing SIRT1 activity (Nisoli E et al., 2005). Fasting or Caloric restriction in obese patients leads to increase in SIRT1 and expression of genes encoding proteins involved in eNOS (Civitarese AE et al., 2007). Obesity is medical condition accompanied by the amount of fat store in body and the extent of obesity depends on the amount of calories consumed vs. calories burned and is depend on the fraction of white adipose tissue (WAT) vs. brown adipose tissue (BAT). The adipose organ is consist of white adipocytes and brown adipocytes in humans. Although WAT store energy and BAT is for energy expenditure (Kahn CR, 2007) but with aging, fat accumulates in different parts of the body viz. bone marrow, muscle and liver and these result in development of various disease such as osteoporosis, insulin resistance and type 2 diabetes (Cartwright MJ et al., 2007; 33. Rosen CJ and Bouxsein ML, 2006). In an experiment conducted on 3T3-L1 mouse preadipocyte model, SIRT1 was shown to repress activity of PPAR-γ to stimulate adipogenesis and increase lipolysis. Although, SIRT1 inhibit proliferation of adipocytes and beta-catenin (such as Wnt-1, Wnt-3a), also inhibit adipogenesis (Fu M et al., 2005). Another sirtuin class, SIRT2 stimulates proliferation of adipocyte by regulating Foxo1 activity (Jing E et al., 2007) and this experiment concluded that 3T3-L1 model demonstrated that SIRT2 overexpression inhibited proliferation whereas reduction in SIRT2 regulate adipogenesis.

1.3. SIRT1 and its targets

SIRT1 deacetylates various targets that stimulate apoptosis in turn leads to stress resistance. For example, during caloric restriction or fasting there is increase in SIRT1 mRNA and protein levels in brain, liver, and fat of rodents (Cohen HY et al., 2004; Rodgers JT et al., 2008; Rodgers JT et al., 2005) result in alterations of metabolism and nutrient availability thus SIRT1is a mediator between the changes in nutrient availability and the physiological response, and its depend on NAD^+ level.

SIRT1 deacetylates lysine residues 1020 and 1024 by inhibiting the activity of p300 (Bouras T, et a, 2005) because p300 regulate gene

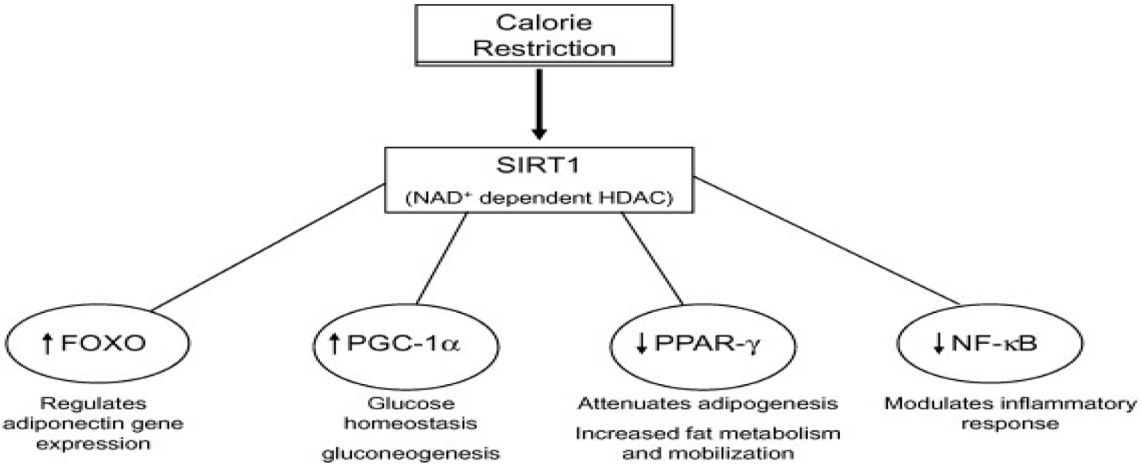

Fig. 2. Physiological response of SIRT1 targets.

expression. In muscle cells, SIRT1 interact with acetyltransferase (PCAF and GCN5), where it plays a significant role in the formation of a complex with the transcription factor MyoD and SIRT1 deacetylates this complex by inhibiting muscle gene expression (Fulco M et al., 2003). It has been stated that SIRT1 activator decrease/adipocyte proliferation (Backesjo CM et al., 2006).Various studies identify that SIRT1 activity in tissues such as pancreatic β cells was important for age-associated metabolic disorders like type 2 diabetes. However, acetylation of the insulin receptor substrate (IRS-2) regulate insulin signaling (Zhang J, 2007).

1.4. Adipogenesis and SIRT1

Adipose tissue is an endocrine organ consist of fibroblasts, endothelial cell, pre-adipocytes, cytokines (adipokines and adipocytokines) that regulate the paracrine action on the body. However, during obesity the adipose tissue undergoes pathological change due to absorption of fat, inflammation in turn leads to overexpression of adipocytes in relation to leaner individuals (Farmer SR, 2006).Although adipogenesis mechanism is regulated by PPAR-γ in which the pre-adipocyte differentiates into a mature adipocyte. Recent studies revealed that PPAR-γ act as a transcriptional factor by regulating adipogeneic mechanism by producing fat cells when they over expressed in mouse fibroblast and also involved with both brown and white fat depots.

PPAR-γ interacts with PPAR-gamma-coactivator 1-α (PGC-1α) that act in conjugation with nuclear respiratory transcriptional factor −1, FOXO1, ERRα, which promotes BAT development, maintain thermogenesis (Lin J et al., 2005; Uldry M et al., 2006) and stimulate pyruvate dehydrogenase kinase4 (PDK4), which inactivates pyruvate dehydrogenase and prevents pyruvate entry into the TCA cycle.

It has been stated that SIRT1 and wnt signaling have been shown to attribute adipogenesis. However wnt signaling inhibit proliferation of stem cells and induction of PPAR-γ by incorporating the wnt ligands, Cyclin D1in preadipocytes that inactivates adipogenesis pathway (Wallace DC, 2005).

1.5. Regulation of metabolism in obesity

Cells mainly acquire energy for cellular respiration from mitochondria. However dysfunctioning of mitochondria leads to various diseases in metabolic syndromes (Petersen KF et al., 2003) such as insulin resistance. Insulin resistance occurs due to less oxidative capacity in mitochondria and decrease in mitochondrial gene expression (Mootha VK et al., 2003) PPAR-γ is a coactivator (PGC-1α) gene linked with mitochondria and it activity is regulated by SIRT1 (Bordone et al., 2007; Rodgers JT and Puigserver P, 2007; Sparks LM et al., 2005). SIRT1 deacetylates PGC-1α, FOXO1 by mediating cellular response in liver to regulates gluconeogenesis (Rodger JT et al., 2005) and inhibit glycolysis through gene transcription.

2. Conclusion

Obesity consist a major health problem in developed and developing countries that has reached substantial morbidity. Obesity is a chronic disorder associated with excessive accumulation of fat in adipose tissue and concomitant formation of blood vessels that affecting both adults and children health and has been recognized as major risk factor for development of various disorder such as cancer, cardiovascular disease, metabolic syndrome, hypertension and diabetes mellitus. Recent evidences suggest that NAD^+ dependent sirtuins SIRT1 plays an essential role in regulation of metabolic activity of lipids and glucose in live but perform distinct activity in chronic and acute inflammation by deacetylating proteins. Additionally they have impaired activity in animal and human obesity due to decrease in glucose activity, high calorie intake by regulating adipogenesis program. In an experiment conducted on transgenic mice proved that the activity and expression of certain SIRT1 enzymes decreases in adipose tissue in turn lead to obesity. It has been stated that sirtuins appear to be therapeutic target for the treatment of obesity and related medical disorders by activating and inhibiting SIRT1 and related enzymes. Increasing activity of SIRT in adipose tissue by identifying natural compounds or by increasing level of NAD^+, a substrate for sirtuins.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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