Chapter 3

Sirtuins in Adipose Tissue Metabolism

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Abstract

Obesity, a complex metabolic disorder linked to the development of several diseases, is characterized by both hypertrophy and hyperplasia of adipocytes. While white adipose tissue (WAT) is an energy storage site, brown adipose tissue (BAT) activation generates heat from nutrients by non-shivering thermogenesis. The human orthologue of silencing information regulator 2 (Sir2) which was recognized as a regulator of life span in *S. cerevisiae*, includes seven sirtuins which are NAD^+-dependent protein deacetylases distributed in different subcellular compartments. Sirtuins, particularly Sirt1, have emerged as important nutrient sensors and regulators of metabolism. Sirt1 has been shown to play a role in retarding the expansion of WAT while stimulating both differentiation and activation of brown adipose tissue as well as browning of WAT. This chapter focuses on the role of sirtuins in adipose tissue biology, their implications in obesity and potential as therapeutic targets.

Keywords: sirtuins, white adipose tissue, brown adipose tissue, adipogenesis, metabolic control, obesity

1. Introduction

Adipose tissue is a functionally diverse organ with remarkable plasticity to adapt to changes in energy balance and contribute to systemic regulation of metabolism. It is capable of expanding in response to over-nutrition preventing ectopic fat deposition in non-adipose tissues, as well as mobilizing stored lipids during starvation or energy demand. Apart from its storage function, its ability to produce multiple adipokines as an endocrine organ, influences functions of other metabolic tissues. The ability of adipose tissue to respond to changes in energy balance is finely regulated by molecular mechanisms linked to nutrient response and

the redox status of the tissue. Sirtuins are a group of NAD^+-dependent protein-deacetylating enzymes that play a key role in metabolic homeostasis. They influence genome stability, transcription and activity of several enzymes contributing to epigenetic regulation and act as key nutrient sensors.

Acetylation and deacetylation of histones and other DNA associated proteins are key epigenetic processes that can influence chromatin structure regulating the transition between highly condensed and transcriptionally less active heterochromatin state to loose and transcriptionally active euchromatin structure [1]. The extent of acetylation of histones depends, on one hand, on the balance between the activity of acetyl transferases such as histone acetyl transferase and deacetylases such as histone deacetylases (HDACs) [2, 3] and on the other hand on acetyl CoA which is an important metabolite at the junction of several metabolic pathways. Phylogenetically, eukaryotic HDACs are ancient proteins comprising of two subfamilies of proteins with different structure and function [4, 5]. While the enzymes belonging to the classical HDAC family are generally Zn-dependent enzymes which remove acetyl group from lysine residues on acetylated protein substrates with the addition of a water molecule, those belonging to the sirtuin family remove acetyl moieties bound to protein substrates to another substrate viz. NAD^+ cleaving it to nicotinamide and *O*-acetyl ADP–ribose. So far 11 members of the classical HDAC enzymes, subdivided into three classes (HDAC I, III and IV), and 7 members of sirtuins belonging to HDAC class III family have been identified.

Sirtuins, particularly SIRT1, play a key role in adipogenesis of white adipose tissue (WAT) and browning of WAT, metabolism of glucose and fat, insulin sensitivity, control of inflammation and energy homeostasis. Dysregulation of these physiological processes have major implications in the development of obesity and related metabolic diseases. The role of sirtuins in the regulation of adipose tissue biology and its implications in the development of obesity form the subject matter of this chapter. A number of reviews on the structure and functions of various sirtuins and their implications in aging and several pathological conditions are available [6–11].

2. Sirtuins in adipose tissue biology

2.1. Biochemistry and molecular biology of sirtuins

2.1.1. Classification and tissue distribution

Interest in understanding the role of sirtuins in mammalian system was driven by findings in calorie-restricted conditions in model organisms. The discovery of a protein in yeast, referred to as yeast-silencing information regulator-2 (Sir2) [12] followed by the demonstration of its localization in the nucleolus and telomeres [13] and low histone acetylation level in the genetic loci highlighted the importance of this group of proteins in regulating chromatin structure in specific loci. These findings were followed by demonstration of the importance of the protein in regulating yeast lifespan [14] and identification of Sir2 as an NAD-dependent histone deacetylase [15]. This revealed the connection between a molecule involved in gene

silencing and cellular metabolism and led to establishing sirtuins as important epigenetic regulators. This was followed by identification of *Sir2* orthologues in mammalian systems; these were demonstrated to be NAD^+-dependent protein deacetylating enzymes that are highly conserved across bacteria to humans.

On the basis of sequence similarity, mammalian sirtuins are classified into four classes, class I–IV. Mammalian SIRT1–3 belong to class I, SIRT4 to class II, SIRT5 to class III and SIRT6 and 7 to class IV (**Table 1**) [9, 16]. All these enzymes share a conserved catalytic core structure, but they differ in their enzymic activity. While class I sirtuins (SIRT1–3) show robust deacetylase activity in vitro, SIRT4–7 show weak deacetylase activity; SIRT4 shows mono ADP–ribosyl transferase activity and SIRT2, 3 and 6 exhibit both deacetylase and ribosyl transferase activity. SIRT5 removes succinyl, malonyl and glutaryl groups from acylated protein–lysine residues. SIRT6 is more efficient in removing long chain fatty acyl groups such as myristoyl and palmitoyl groups. The enzymic reaction proceeds through the formation of a ternary complex involving acetyl protein substrate and NAD at the active site, which decomposes to form deacylated protein, nicotinamide and 2-*O*-acetyl-ADP ribose. They also differ in tissue distribution and subcellular localization (**Table 1**) [6, 9]. SIRT1 is expressed in metabolic tissues such as liver, muscle, adipose tissue and other organs such as heart, brain, pancreas; it is localized mainly in the nucleus, but shuttles from nucleus to cytosol. SIRT2, primarily a cytosolic protein, is highly expressed in heart, brain and skeletal muscle. SIRT3–5 are expressed in mitochondria. SIRT3 and 5 are mainly expressed in kidney, brain, liver and heart. In contrast to white adipose tissue, brown adipose tissue (BAT) expresses SIRT3. SIRT4 is expressed in heart, liver, pancreas and vascular smooth muscle. SIRT6 and 7 are localized predominantly in the nucleus. While SIRT6 is expressed in brain, liver and muscle, SIRT7 is mainly found in liver and spleen.

2.1.2. Biological effects of sirtuins

Mammalian sirtuins influence various cellular processes such as chromatin silencing, cell cycle regulation, differentiation and survival, mitochondrial biogenesis, metabolism, inflammation and stress response. While most studies in model organisms indicate a role for sirtuins in mediating the increased longevity affected by calorie restriction [17], a similar role for mammalian sirtuins is debated [18]. Sirtuins deacetylate transcription factors and regulate their activities either by influencing their cytoplasmic-nuclear distribution, their binding to DNA or changing their interaction with regulatory proteins.

SIRT1 is by far the best characterized among all mammalian sirtuins. It has been linked to hypothalamic control of energy balance [19], has a role in adipogenesis and fat mobilization, as well as regulation of carbohydrate and lipid metabolism [6, 7]. SIRT1 promotes vasodilation and regenerative function in endothelial and smooth muscle cells of vascular wall by targeting eNOS for deacetylation [20]. In cardiomyocytes, SIRT1, 3 and 7 play a critical role in promoting cardiomyocyte resistance to stress and toxicity [21].

Important targets of SIRT1 include p53, forkhead box type O transcription factors (FOXO), PPARγ co-activator-1α (PGC1α), NFkB, androgen receptor and their co-regulatory molecules (**Table 1**). Apart from its effect on PGC1α, a master regulator of mitochondrial biogenesis,

	Sirt 1	Sirt 2	Sirt 3	Sirt 4	Sirt 5	Sirt 6	Sirt 7
Class	I	I	I	II	III	IV	IV
Subcellular location	Nucleus, cytoplasm	Cytoplasm, nucleus	Mitochondria	Mitochondria	Mitochondria	Nucleus	Nucleolus
Tissue	Liver, heart, brain, pancreas, muscle, adipose tissue	Heart, brain, skeletal muscle	Brown adipose tissue, kidney brain, heart, liver	Vascular smooth muscle, skeletal muscle, heart, liver, pancreas	Brain, heart, muscle, liver, kidney	Brain, liver, muscle	Liver, spleen
Activity	Deacetylation	Deacetylation	Deacetylation	ADP-ribosylation	Deacetylation, demalonylation desuccinylation	Deacetylation, ADP-ribosylation	Deacetylation
Target	PGC1-α, PPARγ, PPARα, FOXO1, FOXO3, p53, notch, NF-kB, HIF-1α, LXR, FXR, SREBP1c	Tubulin, PEPCK, FOXO-1,PAR-3	LCAD, HMGCS-2, SOD-2, GDH, IDH2	GDH, Malonyl CoA decarboxylase	CPS1	H3KK9, H3K56	SIRT 1
Biological effects (WAT)							
Adipogenesis	Inhibition	Inhibition					Stimulates
Lipogenesis	Inhibition (decreases AC1)			Stimulates malonyl decarboxylase			
Lipolysis	Stimulates (FOXO1, ATGL)	Stimulates					
β-oxidation							
Oxphos							
Glucose metabolism	Improves insulin sensitivity				Decreases insulin sensitivity		
Inflammation	Decreases				Decreases		Increases
Adipokines	Increases adiponectin Decreases leptin		Increases adiponectin			Increases adiponectin	Decreases leptin

	Sirt 1	Sirt 2	Sirt 3	Sirt 4	Sirt 5	Sirt 6	Sirt 7
Biological effects (BAT)							
Brown adipogenesis			Stimulates (expressed more in BAT than WAT)		Stimulates (expressed more in BAT than WAT)		Inhibits (expressed more in BAT than WAT)
Browing	Stimulates						
Whitening	Inhibits						
β-oxidation	Stimulates		Stimulates				
Oxphos	Stimulates mitochondrial biogenesis		Stimulates				
Thermogenesis	Stimulates		Stimulates				Inhibits
Glucose metabolism	Improves glucose tolerance			Increases on cold exposure		Increases glucose uptake	Decreases glucose tolerance
Effects on sirtuins							
Obesity	Decreased		Decreased	Increased	Decreased?	Decreased	Increased/ decreased
CR	Increased		Increased	Decreased (?)		Increased	Increased
Gastric banding surgery	Increased			Increased			
References	[6, 7, 11, 31, 52, 53, 77, 78, 100, 102]	[6, 7, 11, 26, 31]	[6, 7, 11, 27, 31]	[6, 7, 11, 31, 65, 66]	[6, 7, 11, 31]	[6, 7, 11, 31]	[6, 7, 11, 31, 108]

Table 1. Sirtuins – targets, enzymic activity and biological effects.

SIRT1 acts on several transcription factors like estrogen like receptors, the nuclear respiratory factors 1 and 2 to induce mitochondrial gene expression [22].

SIRT1 appears to directly block lipid anabolism by interfering with PPARγ and LXR signaling. The repressive effect of SIRT1 on PPARγ activity requires the formation of a co-represssor complex that involves NCoR1 [23]. SIRT1 also has a role in reverse cholesterol transport; it stimulates cholesterol efflux from macrophages and the hepatic conversion of cholesterol to bile acids through LXR [24] . It is also present in the cytosol of many cell types and regulates major cytoplasmic enzymes such as acetyl CoA synthase and eNOS by deacetylation [20].

Compared to SIRT1, not much is known about the physiological effect of other mammalian sirtuins. SIRT2 shows similarity to SIRT1 in several of its biological effects. It appears to increase hepatic glucose which is beneficial in starving conditions where SIRT2 activity increases. While it suppresses glycolysis by deacetylating and destabilizing glucokinase, it activates gluconeogenesis by enhancing the action of a key gluconeogenic enzyme PEPCK by its deacetylation [25]. It also appears to have a role in the control of microtubule stability and cell cycle oscillations by deacetylating α-tubulin [26].

SIRT3 is a major regulator of mitochondrial function; it deacetylates several mitochondrial proteins which are critical in mitochondrial oxidative metabolism. Calorie restriction increases activity of SIRT3 which alters the mitochondrial acetylome [27, 28]. SIRT4 is a mitochondrial matrix protein with remarkable ADP-ribosyltransferase activity [29]. It is reported to regulate insulin secretion [30], the activity of glutamate dehydrogenase, and serves as a metabolic regulator by inhibiting the activity of several metabolic enzymes such as pyruvate dehydrogenase opposing the effect of SIRT3 [31]. Although recent studies have identified several SIRT5 target proteins, not much is known about its biological function. SIRT5 appears to play a role in energy homeostasis and free radical metabolism [32]. SIRT6 deficient mice aged prematurely and its overexpression increased life span of male mice apparently by altering IGF signaling [31].

2.1.3. Regulation of sirtuins

Sirtuins are regulated in response to nutritional and metabolic challenges, oxidative stress, and inflammation in a cell and tissue specific manner. They are subject to transcriptional control, post-transcriptional regulation by miRNA and post-translational modulation [31]. These regulatory events can either alter the levels of each sirtuin or their enzyme activity or both. Their activity can be modulated either directly by post-translational modifications(PTMs) such as phosphorylation and acetylation, protein interactions and by compounds that activate them, or indirectly by modulating NAD^+ levels. The substrates themselves appear to regulate sirtuin expression indicating the possible formation of feedback regulatory loops.

Some of the key factors involved in metabolic homeostasis that cause upregulation of SIRT1 include CREB, FOXO1, FOX3a, C/EBPα, PPARα and PPARβ/δ while the negative regulators include ChREBP, C/EBP. NFkB, EGR1, APE1 positively regulate transcription of SIRT1 during stress conditions. SIRT1 in turn can modulate the activity of several of these transcription factors. The enzymatic activity of SIRT1 is enhanced by post-translational modification by phosphorylation [33] and SUMOylation (Lys734) [34]. The activity of SIRT1 can also be controlled

through interaction with different protein complexes such as DBC1 (nuclear protein deleted in breast cancer-1), AROS (active regulator of SIRT1) and NCoR1 [35, 36]. SIRT1 can also be activated indirectly by either increasing NAD^+ synthesis from NAD^+ precursors like nicotinic acid, NAM, nicotinamide riboside or decreasing NAD^+ consumption by two alternate enzyme families, PARP and cADP ribose synthase [37]. SIRT1 can enhance its own activity by auto-deacetylation. This is inhibited by SIRT7 suggesting coordinated action of different sirtuins [38]. SIRT1 is inhibited by NADH which competes with NAD^+ [39] and by nicotinamide [40]. *In vitro* studies using malignant cell lines, have reported the role of different miRNAs in the post-transcriptional regulation of SIRT1 [31]. Mir34a is reported to regulate SIRT1 at different levels; it inhibits translation of SIRT1 mRNA; it indirectly suppresses transcription and enzyme activity of SIRT1 by modulating the levels of NAD through regulation of the biosynthetic enzyme nicotinamide phosphoribosyl transferase [41].

Unlike SIRT1, information on the regulation of other sirtuins is limited. Cyclin(E-Cdk2 and A-Cdk2) mediated phosphorylation at S331 inhibits SIRT2 activity whereas Erk1/2 enhanced its activity [31]. Cyclic AMP–PKA pathway, which is activated in response to various stimuli, causes upregulation of SIRT3 expression through PGC1α. cAMP may also activate SIRT3 by direct binding [31]. Activated AMPK also positively regulates SIRT3 by increasing NAD. Similar to SIRT3, expression of SIRT5 is also upregulated by PGC1α, while AMPK appears to negatively regulate its expression [31]. Several transcription factors and miRNAs appear to regulate expression of SIRT6. While Nuclear Respiratory factor 1 (NRF-1) and co-activators induce SIRT6 expression during nutrient deprivation, cAMP signaling reduces SIRT6 expression. A relation between SIRT6 and mir122 has also been suggested [31].

2.2. Sirtuins regulate WAT development and metabolism

Adipose tissue is classified into white adipose tissue (WAT) which serves as the principal energy storage organ and brown adipose tissue (BAT) whose principal function is maintaining temperature by non-shivering thermogenesis. A third category includes beige or brite (brown in white) adipocytes within WAT which can potentially differentiate into cells of brown like phenotype.

2.2.1. Sirtuins and WAT development

The cellular and molecular mechanisms that govern the adipocyte life cycle have been extensively studied [42–45]. Both white and brown adipocytes develop by a highly regulated process of differentiation of mesenchymal stem cells (MSC). During the early phase of adipogenesis the pluripotent MSCs are committed to unipotent pre-adipocytes which in the latter phase undergo terminal differentiation acquiring the characteristic phenotype and functions of mature adipocytes. The complex process of adipocyte differentiation is coordinated by myriad factors. Isoforms of bone morphogenetic protein, BMP2 and BMP4 are the key positive regulators of commitment to white pre-adipocytes [46, 47]. This early phase of differentiation is also subject to negative regulation by several transcription factors including members of GATA and Forkhead family, Wnt and Notch signaling, Kruppel-like factors 2 and 7 (KLF2, KLF7) and CHOP proteins [48].

The differentiation of white pre-adipocytes to mature adipocytes is mediated by multiple transcription factors. The key transcription factors involved are CCAAT enhancer binding protein (C/EBP), PPARγ and sterol-regulatory element binding protein 1 (SREBP1) [43]. C-EBP, which exists in six different isoforms, is activated and translocated to the nucleus in response to cAMP mediated signaling [43]. Hormones induce transient expression of C/EBPβ and C/EBPδ which upregulate expression of PPARγ and C/EBPα [43] PPARγ, (particularly the isoform PPARγ1) that belongs to the nuclear receptor superfamily, heterodimerises with retinoid receptor α (RXRα), another nuclear receptor, and binds to DNA to promote expression of adipocyte specific genes such as leptin, adiponectin, FABP4, and perilipin. Activation of C/EBPα leads to transcriptional activation of several genes encoding proteins such as GLUT4, SCD1, FABP4 which are critical in establishing adipocyte phenotype [43].

All seven sirtuin genes are expressed in human and rodent WAT. A difference in their level of expression, particularly a reduction in SIRT1, has been observed, in experimental obese models as well as obese human subjects [11]. Studies in experimental model systems suggest that sirtuins, particularly SIRT1, are negative modulators of WAT adipogenesis. Overexpression of SIRT1 decreased accumulation of fat while its knockdown increased fat accumulation in 3T3L1 cells undergoing differentiation [23]. Resveratrol, an activator of SIRT1 reduces osteoblastic differentiation of MSC to adipocytes [49]. SIRT1 is upregulated in WAT in calorie-restricted mice model in which there was significant reduction in fat mass [50, 51]. Further, transgenic mice overexpressing SIRT1showed lower body weight and reduction of fat mass [52], while ablation of SIRT1 in WAT resulted in gain in body weight, increase in fat mass and an increase in the size of individual adipocytes [53]. Studies using bone marrow-derived MSC with SIRT1 deletion showed impaired self- renewal and differentiation to osteoblasts without significantly affecting their differentiation to adipocytes [54]. In the light of these observations it has been suggested that although SIRT1 inhibits adipocyte differentiation, its expression is critical for maintenance of MSC pool [11].

PPARγ is an important substrate for SIRT1 [55]. SIRT1 dependent deacetylation of lysine residues (268 and 293 K) on PPARγ is critical in the regulation of its transcriptional activity by its co-repressors NCoR and SMRT. Sirt1 can thus inhibit white adipogenesis by suppressing the transcriptional activity of PPARγ by promoting the binding of its co-repressors NCoR and SMRT [23]. Further, C/EBPα, a PPARγ dependent factor, regulates the expression of SIRT1 during adipogenesis [56]. miRNAs can also regulate effects of SIRT1 on adipogenesis. For example, mir 146b can promote adipogenesis by suppressing SIRT1-FOXO1 cascade [57]. SIRT2, the predominant sirtuin in adipose tissue, has also been shown to inhibit adipocyte differentiation by deacetylating FOXO1 and enhancing its repressive interaction with PPARγ [58, 59]. Unlike SIRT1 and SIRT2, SIRT7 knockdown in human pre-adipocytes reduced lipid content and the number of $FABP4^{+}$ differentiated adipocytes indicating a contrasting effect of SIRT7. Further, SIRT7 knockout mice had significantly reduced WAT and increased SIRT1 activity. This suggests that SIRT7 influences adipogenesis in mice by inhibiting autocatalytic activation of SIRT1, further highlighting the importance of cross talk among sirtuins in the control of adipose tissue maintenance [38].

2.2.2. Sirtuins and WAT metabolism

During times of positive energy balance, storage of lipids as triglycerides in lipid droplets in adipocytes leads to expansion of adipose tissue. It leads to changes in the levels of adipokines such as leptin and adiponectin that affect metabolic functions of other organs particularly liver, muscle and brain, which in turn can affect the adipose tissue function [43, 45]. The stored lipid is mobilized in response to hormones and systemic energy needs during periods of negative energy balance. Metabolism of adipose tissue is thus linked with that of other tissues. SIRT1 appears to serve as an important metabolic switch through which adipose tissue and other metabolic organs respond to energy needs [8].

When energy stores are high, excess nutrients particularly glucose and amino acids are used to synthesize fatty acids de novo primarily in liver and are exported to WAT where they are stored as TG [6] SIRT1 deacetylates sterol-responsive element binding protein 1c (SREBP1c) causing reduction of its transcriptional ability and suppression of fatty acid synthesis [6]. Further, by increasing PGC1α-mediated mitochondrial biogenesis, SIRT1 facilitates fatty acid oxidation. SIRT1 promotes gluconeogenesis in the liver through deacetylation and activation of PGC1α and FOXO1, and increasing expression of gluconeogenic enzymes [22] and inhibits glycolysis [6] This increases hepatic production of glucose during fasting. Apart from SIRT1, SIRT6 also has been shown to repress glycolysis in liver [31]. Further, SIRT1, by deacetylating STAT3, reduces its repressive effect on gluconeogenesis [60].The hepatic effects of sirtuins can thus affect nutrient flux into the adipose tissue.

Sirtuins are not only critical in WAT adipogenesis, they also play a key role in maintaining the functions of differentiated adipocytes by regulating the expression of several PPARγ-responsive genes involved in metabolism. Activation of SIRT1 reduces expression of acetyl coA carboxylase and other lipogenic genes involved in the de novo synthesis of FAs in pre-adipocytes. Multiple studies support the role of PPARγ in regulating adipose tissue metabolism [61]. Over-expression of a dominant negative form of PPARγ downregulates the expression of key genes involved in lipid metabolism, insulin signaling and decreases lipid content in 3T3L1 differentiated adipocytes [62]. Further, selective ablation of PPARγ in mature white and brown adipocytes results in adipocyte death without any effect on pre-adipocyte differentiation indicating the requirement of PPARγ for maintenance of differentiated functions of adipocytes [63]. Insulin dependent glucose uptake in the adipocyte takes place through the GLUT4 transporter. Expression of GLUT4 gene is regulated by PPARγ. SIRT1 appears to regulate glucose–induced secretion of insulin by transcriptional repression of UCP2 which uncouples mitochondrial ATP production [64]. SIRT1 by deacetylating SREBP1, destabilizes and reduces its occupancy on the lipogenic gene promoters suppressing fatty acid synthesis [6]. Although SIRT1 inhibits lipogenesis in WAT, SIRT4 appears to have an opposite effect. Deletion of mitochondrial SIRT4 decreased lipogenesis apparently by regulating malonyl CoA decarboxylase, thereby altering the level of malonyl CoA that represses fatty acid oxidation [65, 66]. While an increase in SIRT4 in fed state results in deacetylation and inactivation of malonyl CoA decarboxylase resulting in enhanced FA synthesis, during fasting, reduction of SIRT4 expression

leads to activation of malonyl CoA decarboxylase resulting in enhanced lipid oxidation. It therefore appears that SIRT4 exhibits a dual effect regulating anabolism and catabolism of fatty acids [65]. SIRT6 also appears to regulate lipogenesis. In SIRT6 overexpressing mice, expression of diacylglycerol acyl transferase a key enzyme involved in TG synthesis was down regulated along with certain PPARγ responsive genes involved in lipogenesis [31, 67].

2.2.3. Mobilization of depot fat

During periods of negative energy balance, the triglycerides stored in the lipid droplets, are hydrolysed to FFA which are released into circulation. In the basal state or during TG synthesis, perilipin, the structural protein on lipid droplet, is bound to protein CGI-58 (comparative gene identification-58) which is a co-activator of the adipose triglyceride lipase (ATGL). In response to cAMP dependent PKA-mediated phosphorylation of perilipin, CGI-58 is released leading to activation of ATGL [68]. Activated ATGL moves to the lipid droplet membrane surface to hydrolyse TG to diacyl glycerol. Further activation of hormone sensitive lipase (HSL) by PKA mediated phosphorylation causes binding of HSL to perilipin and continues lipolysis forming monoacyl glycerol which is acted upon by another specific monoacyl glycerol lipase (MGL) forming glycerol and FFA which are released to plasma for systemic utilization.

Unlike its suppressive effect on adipogenesis in WAT, SIRT1 appears to promote mobilization and utilization of depot fat. Overexpression of SIRT1 in differentiated 3T3L1 cells resulted in decreased triglyceride levels and increased release of FFAs [23], while knockdown of SIRT1 decreased basal and stimulated lipolysis in adipocytes in culture. In *in vivo* studies using mice receiving high fat diet, activators of SIRT1 such as resveratrol reduced fat mass [69]. Further, over expression of SIRT1 inhibited diet induced accumulation of fat [6, 31, 52]. SIRT1 regulates the expression of ATGL gene and thereby lipolysis in adipocytes through modulation of the acetylation and transcriptional activity of FOXO1 [70]. SIRT2 also appears to show similar effect on fat mobilization [58, 59].Although sirtuins influence mitochondrial oxidative metabolism in other metabolic tissues such as liver, their role in WAT mitochondrial metabolism is poorly understood.

2.3. Role of sirtuins in BAT development and browning of WAT

Unlike white adipogenesis, BAT biogenesis involves BMP7-stimulated commitment of Myf 5^+ cells to brown pre-adipocytes that mature into mitochondria–rich brown adipocytes.BMP7 stimulation of progenitor cells leads to down regulation of early adipogenic inhibitors such as Pref1, Nectin, Wnt signaling molecules [43]. This is followed by upregulation of transcription factors such as PPARγ and C/EBPα which cause upregulation of expression of PRDM16, a key factor involved in adipocyte–myocyte switch through activation of expression of BAT specific genes (PGC1α, UCP-1, ZIC1) and downregulation of myogenic genes such as Myf5 and MyoD or myogenin [43]. This leads to increased biogenesis of mitochondria. PRDM16 is a 140 kDa protein that binds and activates the transcriptional function of PPARγ and PGC1α. PGC1α co-activates PPARγ-RXRα heterodimer stimulating the expression of BAT-specific genes UCP1and UCP3.

The ability of human white adipocytes to acquire brown fat-like phenotype, termed browning, in response to β-adrenergic stimulation, cold exposure [43] and by several molecules such as muscle derived irisin [71, 72] liver derived FGF21 [73] and small molecules such as β-aminoisobutyric acid [74] has been observed. These type of cells called beige or brite adiopcytes express genes involved in thermogenesis such as UCP1, deiodinase type II and PGC1α in response to stimulation of β3–adrenergic receptors [43].

Sirtuins also appear to play a role in the differentiation and function of BAT. Like WAT, brown adipose tissue also has been shown to express all the members of the mammalian SIRT family [11]. While the relative level of expression of SIRT3 and 5 are higher, that of SIRT1 and 7 are lower in BAT than those in WAT. Calorie restriction (CR) and cold exposure upregulated the expression of SIRT3 present in the mitochondria in BAT [75]; SIRT1 and SIRT2 also showed an upregulation under such conditions. Conversely, SIRT3 is down regulated in BAT in high fat diet induced obese mice. SIRT1 also appears to have a role in differentiation of pre-adipocyte to brown adipocytes. It appears that SIRT1 influences BAT differentiation through repression of the MyoD-mediated myogenic gene expression signature and stimulation of PGC-1α mediated mitochondrial gene expression [76]. SIRT1 appeared to improve glucose homeostasis in SIRT1 transgenic mice and brown adipocytes derived from them due to an enhanced response of brown adipocytes to β3-adrenergic stimuli rather than differences in differentiation status [77]. Of the different sirtuins, SIRT3 appeared to be critical in the differentiation of brown adipocytes. SIRT3 has been shown to activate PGC1α mediated thermogenic response in differentiating brown adipocytes.

Brown remodeling of white fat in response to cold exposure is shown to be regulated by SIRT1-dependent deacetylation of PPARγ. SIRT1-dependent deacetylation of Lys 268 and Lys 293 of PPARγ is required to recruit the co-activator PRDM16 to PPARγ, leading to upregulation of BAT-specific genes and repression of WAT genes [78].In response to different environmental stimuli, SIRT1 can differentially modulate PPARγ in WAT. SIRT1 inhibits PPARγ through local modulation of acetylation status of histones and recruitment of co-repressor NCoR in response to caloric restriction; but on cold exposure, it directly enhances PPARγ signaling through deacetylation of PPARγ itself [79]. SIRT1 deficiency in mice results in accumulation of lipid droplets and reduction of mitochondrial content in BAT indicating a role for SIRT1 in the white remodeling of BAT which appears to occur in obese conditions [80].

2.4. Sirtuins and obesity

Grossly elevated fat stores in adipose tissue with hypertrophic or hyperplastic adipocytes and concomitant development of blood vessels result in obesity. The relevance of sirtuins in adipose tissue development and metabolism and their effects on metabolism of glucose and lipids primarily in the liver, and insulin function suggest a possible link between sirtuins and obesity.

The level of expression and activity of SIRT1 decrease in adipose tissue in different obesity models. Expression of SIRT1 in adipose tissue of db/db leptin resistant obese mice and in mice fed on HFD was significantly low [53, 81]. Overexpression of SIRT1 in HFD-induced obese animals caused less inflammation and better glucose tolerance. SIRT1 expression in obese pigs

is reported to be lesser than that in lean pigs [82]. Apart from decrease in SIRT1 levels, its function is also affected by changes in its post translational modification in obesity. One of the important post-translational modifications of SIRT1 which has been shown to be affected in obesity leading to inhibition of its nuclear localization is casein kinase mediated phosphorylation of ser-164 which is enhanced in obese and not in lean animals [83]. Unlike SIRT1 which is decreased in WAT in obesity, there is no consensus on the changes in other sirtuins in obese WAT; while some reports show decrease in SIRT2–6, other reports do not show any significant differences between obese and respective controls. But in obese BAT, SIRT1 and SIRT3 are down regulated and SIRT7 is upregulated. It has been shown that mir34a, which regulates the expression and activity of Sirt1, is elevated in obesity [41]. A possible association of sirtuins with obesity and obesity-associated pathological conditions in humans has also been indicated mostly from observational studies [84–88]. There is significant reduction in sirtuins in adipose tissue and other metabolic tissues in obese subjects and that weight loss or long term fasting can result in increase in their expression.

2.4.1. Sirtuins, insulin response and energy homeostasis

Insulin resistance is a hallmark of obesity and a major factor contributing to obesity associated pathological conditions. *In vitro* and *in vivo* studies suggest that SIRT1 regulates insulin response. In insulin resistant cells where SIRT1 is down regulated, induction of SIRT1 expression increased insulin sensitivity [89]. SIRT1 regulated insulin-dependent glucose uptake in adipocytes. Increase in SIRT1 activity improved insulin sensitivity [90]. Adipose tissue-specific SIRT1 knockout mice were reported to be more prone to developing insulin resistance. In experimentally induced diabetic animals, overexpression of SIRT1 increased insulin sensitivity. Mechanistically, SIRT1 effect appears to involve transcriptional repression of protein tyrosine phosphatase 1B gene which is critical in insulin signaling [91] Along with SIRT1in WAT, SIRT3 and SIRT5 contribute to systemic glucose homeostasis. As indicated before, SIRT1 also regulates insulin secretion by β-cells of pancreas by repressing UCP-2 [64]. Inhibition of SIRT1 expression reduced insulin secretion in β-cell lines; conversely overexpression of SIRT1 increased it. *In vivo*, transgenic mice over expressing SIRT1 in pancreatic β-cells showed increase in glucose-stimulated insulin secretion [92]. Further, SIRT1 deficiency impaired insulin secretion apparently by disrupting glucose sensing and impairing response to fluctuations in glucose levels [93].

In addition to its effect on peripheral tissue metabolism, SIRT1 in hypothalamus appears to act as a key regulator of central control of energy homeostasis. Evidence in support of this include (a) increase in the expression and activity of SIRT1 in hypothalamus in both calorie restriction and fasting [19, 94] (b) inhibition of hypothalamic SIRT1 expression, specifically in anorexigenic POMC neurons, resulted in loss of response to leptin and reduced energy expenditure indicating requirement of SIRT1 in POMC neurons for homeostatic defense against diet- induced obesity [95] (c) deletion of SIRT1 expression specifically in orexigenic Agouti-related peptide (AgRP)-expressing neurons, which promotes feeding in response to fasting, decreased AgRP neuronal activity resulting in decreased food intake and body weight [96] (d) Central inhibition of SIRT1 in rodents on a high fat diet caused decreased body weight and increased energy expenditure. This is mediated through increased acetylated-FoxO1-mediated increased production of POMC and its active product αMSH which in turn augmented TRH and T3 levels suggesting a hypothalamic–pituitary-thyroid axis which stimulates energy expenditure [97].

2.4.2. Sirtuins and inflammation in adipose tissue

Inflammation of adipose tissue in obesity is a major contributor to insulin resistance and pathogenesis of the metabolic syndrome [98]. SIRT1 could act as a transcriptional regulator of inflammation in multiple tissues, particularly adipose tissue as well as macrophages and endothelial cells [90, 99]. The levels of SIRT1 is inversely related to inflammation in adipose tissue. SIRT1 expression in human subcutaneous adipose tissue was less in cases where macrophage infiltration was high [100–102]. The decrease in SIRT1 in obese conditions in adipose tissue is suggested to be due to its proteosomal degradation. Activation of C-jun N terminal kinase (JNK1), which is a key component in inflammation associated signaling pathway, leads to phosphorylation of SIRT1, followed by its degradation in proteasomes [53, 103]. The molecular basis of the beneficial effect of SIRT1 on inflammation is related to suppression of NFkB activation [104]. SIRT1 inhibits transcriptional activity of NFkB directly by deacetylating the RelA/p65 subunit of NFkB at Lys 310 [105]. Moreover mir34a dependent decrease in SIRT1 activity can increase NFkB activity [41]. This suggests that SIRT1 and inflammatory signals interact at various levels and that SIRT1 is an important molecular link between nutrients, inflammation and metabolic dysfunction of the tissue. Though not much data on the role of other sirtuins in inflammation in human subjects is available, SIRT5 expression levels also correlate inversely with markers of inflammation [106] Deletion of SIRT7 in mice reduced WAT inflammatory gene expression in HFD induced obesity, suggesting opposing functions for SIRT1 and 7 [107].

2.4.3. Sirtuin activators for therapy

Since sirtuins play an important role in regulation of adipogenesis, and adipose tissue metabolism, pharmacological activation of sirtuins could be a useful approach for the treatment of obesity and related metabolic disorders. Sirt1 is an allosteric enzyme which is regulated by ligand binding. Resveratrol, which is a naturally occurring polyphenol with anti-oxidant property, increased the enzyme activity of SIRT1 by binding to its allosteric site [108]. High throughput screening has identified several small molecular activators of SIRT1 [109]. The most potent of these is SRT1720 which, protects against diet induced obesity [6]. The administration of SRT1720 reduced expression of lipogenic enzymes and reduced hepatic lipid accumulation, it also enhanced oxidative metabolism in skeletal muscle, liver and BAT in mice, protecting from HFD induced obesity and insulin resistance [110]. However, increasing sirtuin activity could result in indiscriminate deacetylation of histones and several other key proteins in different tissues. Sirtuin activating therapies would therefore have to be target specific.

3. Conclusions

Epigenetic modifications have emerged as fundamental modulators of metabolic functions, and sirtuins, a group of class III histone deacetylases, play a key role in this context. In this chapter the regulatory effects of sirtuins on adipose tissue metabolism in both WAT and BAT, and implication of alterations in their expression and activity in obesity, inflammation, and insulin resistance have been highlighted.

In spite of considerable advances in molecular biology of mammalian sirtuins, many questions remain unanswered. Among the different sirtuins, the role of SIRT1 in development and metabolism of white adipose tissue is reasonably well known. Although all the other sirtuins are expressed in WAT, their role in WAT function is not clear. Similarly, the role of SIRT1 and 3 in brown remodeling of white fat has been elucidated, but the regulatory effects of the other sirtuins are still unknown.

Different sirtuins control similar cellular processes in adipose tissue. Unraveling the potential crosstalk and coordination between them will require further study. The significance of this in the possible gene regulatory network and coordinated action among sirtuins in metabolic regulation is evident from the antagonistic interaction between SIRT1 and 7 in adipose tissue metabolism.

Apart from functional differences between WAT and BAT, variations in the status of different depots of WAT are also related to a risk for obesity-associated diseases. It is not clear whether there is any depot dependent variation in sirtuin action.

As the expansion of a vascular tissue like adipose tissue is associated with neovascularization, adipogenesis and angiogenesis are interrelated. Understanding the role of sirtuins in adipose tissue angiogenesis is of paramount importance especially in brown tissue, where both the mitochondrial activity and oxygen demand are high.

Sirtuins appear to be an attractive target for the treatment of obesity and related metabolic disorders. Increasing sirt activity in adipose tissue by identifying natural compounds, or engineering small molecular activators is an area which needs intensive research; increasing intracellular levels of NAD^+, a substrate for sirtuins, is an alternate approach.

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Conflict of interest

The authors declare that there is no conflict of interest.

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