International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jms.htm
2015 Vol. 5 (1) January-April, pp. 14-26/Sudhakar et al.
Review Article

SIRTUINS AND OBESITY RELATED METABOLIC DYSFUNCTION

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ABSTRACT
Obesity is recognized as a major risk factor for type 2 diabetes, cardiovascular diseases and other related metabolic diseases. Recent studies have identified Sirt1, the most conserved mammalian NAD- dependent protein deacetylase belonging to the family of sirtuins as a master regulator of metabolic tissue functions which are deranged in obesity. Sirt1 can regulate the expression of several genes through regulating the activity of transcription factors and their co-activators by regulating their acetylation status. Sirt1 has been shown to play a key role in white adipocyte development and browning of white fat, mobilization of depot fat, insulin secretion and insulin sensitivity, regulation of inflammation and central control of energy homeostasis. Alterations in these physiological processes have major implications in the development of obesity and related metabolic diseases and therefore Sirt1 is emerging as a potential therapeutic target. This review focuses on recent developments on the role of sirtuins particularly Sirt1 in the regulation of adipose tissue biology and its implications in the development of obesity and associated metabolic diseases.

Keywords: *Sirtuins, Sirt1, Obesity, Adipocyte Biology, Transcriptional Regulation, Metabolic Control*

INTRODUCTION
Obesity, associated with increased risk for chronic diseases such as cardiovascular diseases and type 2 diabetes, is a major public health problem. Projections for the next five years indicate approximately 2.3 billion adults will be overweight and over 700 million adults will be obese. The increased fat mass and energy storage in adipose tissue in turn leads to inflammation and insulin resistance. Despite advances in understanding molecular mechanisms of obesity, attempts in combating obesity have been ineffective. The human orthologue of Sir2 (silencing information regulator 2) 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. Investigations carried out during the last decade revealed the importance of sirtuins, particularly Sirt1, as a nutrient sensor and regulator of metabolism. Multiple targets of Sirt1 in different mammalian tissues contributing to tissue physiology have been identified, revealing its tissue specific action. There are a number of reviews on sirtuins dealing with the enzymic properties, physiological and metabolic functions, aging and association with different pathologies (Metoyer and Pruitt, 2008; Lavu *et al.*, 2008; Li, 2013; Guarente 2013). This review focuses on the role of sirtuins in adipose tissue metabolism and examines whether sirtuins could be potential target for controlling fat mass and obesity associated metabolic dysfunction.

Sirtuins
Sirtuins are a group of NAD^+ dependent protein-deacetylating enzymes that are highly conserved from bacteria to humans and play a key role in whole body metabolic homeostasis. In mammals, sirtuin family of enzymes comprises seven Sir2 orthologues ranging from Sirt1 to Sirt7 that share a conserved catalytic core, but differ in their subcellular localization (Dali-Youcef *et al.*, 2007; Michan and Sinclair, 2007). Sirt1 is localized mainly in the nucleus, but shuttles from nucleus to cytosol, where its targets are found (Michishita *et al*., 2005; Tanno *et al*., 2007). While Sirt2 resides in cytoplasm and regulates gene expression by deacetylation of transcription factors that shuttles from cytoplasm to nucleus (Jing *et al*., 2007), Sirt 3,4 and 5 are mitochondrial proteins (Onyango *et al.*, 2002; Schwer *et al.*, 2002; Michishita *et al.*, 2005), and Sirt 6 and7 are nuclear. Apart from their distinct sub-cellular localization, sirtuin family members can also be distinguished by the difference in enzymatic activity. While Sirt1 and 5 are deacetylases (Imai *et al.*, 2000), Sirt 4 is a mono ADP ribosyl transferase (Haigis *et al.*, 2006) and Sirt 2,

3 and 6 exhibit both activities (North *et al*., 2003; Liszt *et al.,* 2005; Shi *et al.*, 2005; Michishita *et al.,* 2008). Sirt 7 is proposed to be a deacetylase (Vakhrusheva *et al.,* 2008) and Sirt 5 acts as demalonylase and desuccinylase (Du *et al.,* 2011). Sirt1 is best characterized among all sirtuins. The enzymatic activity of Sirt1 and downstream pathways are directly coupled to metabolism. In the fed state, an increase in glycolytic activity leads to a reduction in NAD^+ level that subsequently reduces Sirt1 activity, whereas during severe exercise, fasting or calorie restriction, the increase in mitochondrial oxidative metabolism derived from fatty acid oxidation leads to higher NAD^+ levels resulting in an increase in Sirt1 activity. The activity of Sirt1 is inhibited by NADH which competes with NAD^+ (Lin *et al.,* 2004), and by nicotinamide (Bitterman *et al.*, 2002).

Biological effects of Sirtuins: Sirtuins influence a wide range of physiological functions. They are involved in mediating increased longevity produced by calorie restriction. Increased expression of Sirt1 leads to lower cholesterol, blood glucose and insulin levels; it also increases the number of mitochondria in neurons. Sirt1 has been linked to hypothalamic control of energy balance (Cakir *et al.,* 2009); it has a role in adipogenesis and fat mobilization as well as regulation of carbohydrate and lipid metabolism. Sirt1 promotes endothelial dependent vasodilation and regenerative function in endothelial and smooth muscle cells of vascular wall by targeting eNOS for deacetylation (Mattagajasingh *et al.,* 2007). In cardiomyocytes, Sirt1, 3 and 7 plays a critical role in promoting cardiomyocyte resistance to stress and toxicity (Sundareshan *et al.,* 2008). Sirtuins are also expressed in mammalian brain but play very different roles and respond in dissimilar ways to stress and toxicity (Pfister *et al.,* 2008).

Sirtuins deacetylate transcription factors and regulate their activities either by altering their subcellular localization, changing their expression level, altering their binding to DNA or by changing their interaction with regulatory proteins. Sirt1 acts on PPARγ co-activator 1α (PGC 1α), a master regulator of mitochondrial biogenesis and a number of transcription factors like estrogen like receptors, the nuclear respiratory factor 1 and 2 or PPAR to induce mitochondrial gene expression (Rodgers *et al*., 2005). During energy stress, an increased AMP/ATP ratio or ADP/ATP ratio leads to an increase in the enzymatic activity of AMPK which further leads to the phosphorylation of PGC 1α and its activation by Sirt1 (Hardie, 2007). Several hormones such as adiponectin, leptin, and FGF21 acting through this AMPK/Sirt1/PGC1α signaling pathway, enhance mitochondrial metabolism (Chau *et al.,* 2010; Li *et al*., 2011). Other important substrates of Sirt1 include p53, forkhead box type O transcription factors (FOXO), NFκB, androgen receptor and their co-regulatory molecules.

Apart from enhancing lipid catabolism and mitochondrial respiration by deacetylating PGC1α and FOXO, Sirt1 directly blocks lipid anabolism by interfering with PPARγ and Liver X-Receptor (LXR) signaling. The repressive effect of Sirt1 on PPARγ activity requires the formation of a co-represssor complex that involves NCoR1 (Picard *et al.,* 2004). Thus during fasting, Sirt1 associates with NCoR1 and represses PPARγ function favoring fat mobilization. Although PPARγ is a major controller of lipid anabolism in adipose tissue, other nuclear receptors can also perform similar functions in other tissues. LXR α and LXR β can sense oxysterol levels and regulate genes that decrease total body cholesterol level (Kalaany and Mangelsdorf, 2006). LXRs are potent stimulators of anabolism through the induction of SREBP 1C and its downstream targets. Sirt1 deacetylates LXR and increases its transcriptional activity, even though deacetylated Lys residue of LXR makes it more prone to ubiquitinylation and degradation (Ponugoti *et al.,* 2010). Sirt1 also stimulates cholesterol efflux from macrophages to liver and the hepatic conversion of cholesterol to bile acids potentially through LXR suggesting the role of Sirt1-LXR pathway in reverse cholesterol transport (Rodgers and Puigserver, 2007).

Sirt1 also modulates carbohydrate metabolism via deacetylation of transcription factors. CREB, a key transcriptional regulator of gluconeogenic gene expression, is controlled by the co-activator CRTC (Altarejos and Montminy, 2011). Sirt1 activation deacetylates CRTC 2 at Lys628, leading to its ubiquitinylation and proteosomal degradation (Liu *et al.,* 2008). Sirt1 thus attenuates gluconeogenesis, a process that consumes ATP, in an effort to prevent premature energy depletion upon fasting.

The major cytoplasmic enzymes deacetylated by Sirt1 include acetyl CoA synthase and eNOS (Mattagajasingh *et al.,* 2007). Sirt1 also deacetylates the calmodulin binding domain of eNOS, thereby

increasing endothelial nitric oxide level. The activation of eNOS by Sirt1 could be a mechanism by which nutrient scarcity increases energy delivery in tissues. Sirt1 also forms complexes with components of autophagy machine, including Atg 5,7 and 8 and deacetylate them in NAD- dependent manner (Lee *et al.,* 2008).

Modulation of Sirt1 activity: The activity of Sirtuins can be modulated either directly by post translational modifications, protein interactions and by compounds that activate Sirt1, or indirectly by modulating NAD^+ expression by increasing NAD^+ synthesis or decreasing NAD^+ consumption. The activity of Sirt1 can be post translationally modified by phosphorylation (Beausoleil *et al.,* 2004) and SUMOylation (Yang *et al.,* 2007c). Phosphorylated form of Sirt1 is more active and it is achieved by kinases such as cyclinB/Cdk1, JNK1, casein kinase II, and mammalian sterile 20 like kinase I (Yuan *et al.,* 2011a, Guo *et al.,* 2010). Sumoylation of Sirt1 at Lys734 increases its intrinsic deacetylase activity. 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 (Kim *et al.,* 2008; Zhao *et al.,* 2008). Sirt1 activity can be modulated indirectly by increasing NAD^+ synthesis by supplementing NAD^+ precursors like nicotinic acid, NAM or nicotinamide riboside and by decreasing NAD^+ consumption by two major families of alternate enzymes, PARP and cADP ribose synthase (Krishnakumar and Kraus, 2010).

Sirt1 Regulates white Adipose Tissue Development and Metabolism

Adipose tissue growth involves an increase in number and size of adipocytes, the principal fat storing cells in WAT. The cellular and molecular mechanisms that influence the adipocyte life cycle has been extensively studied (Rayalam and Baile, 2012). Mesenchymal stem cells are the precursors of pre-adipocytes which through a series of events differentiate into mature adipocytes. This is accompanied by increase in the expression of adipocyte specific genes concerned with lipid and glucose transport, synthesis and mobilisation of fatty acids and TGs, regulation of insulin sensitivity and endocrine function. Growth and differentiation of adipocytes are controlled by (a)various hormones such as insulin,GH,IGF-1,thyroid hormones and glucocorticoids (b)transcription factors such as PPARγ, CCAAT/EBP, SREBP, Wnt and β catenin, STATs and Kruppel-like factor KLF (c)enzymes involved in lipid metabolism and transporters of glucose (GLUT4) and fatty acids (fatty acid binding protein FABP) and (d) growth factors and cytokines. Concerted action of lipolytic enzymes which are tightly regulated at multiple levels causes fat mobilisation while triggering apoptotic pathways cause apoptosis of adipocytes.

In vitro studies using adipose tissue derived progenitor cells or pre-adipocyte cell lines such as 3T3L1 cells as well as in vivo studies using different experimental animal models such as rodents and pigs suggest that sirtuins, particularly Sirt1, is a negative modulator of WAT adipogenesis. In 3T3L1 cells undergoing differentiation, overexpression of Sirt1 resulted in accumulation of much less fat while its knockdown caused increase in fat accumulation suggesting an inhibitory effect of Sirt1 on adipogenesis (Picard *et al.,* 2004). Activation of Sirt1 by resveratrol has also been shown to reduce osteoblastic differentiation of mesenchymal stem cells to adipocytes (Bäckesjö *et al.,* 2006). Sirt1 is reported to be upregulated in WAT in calorie- restricted mice model in which there was significant reduction in fat mass (Cohen *et al.,* 2004; Chen *et al.,* 2008). Further evidence suggesting that Sirt1 controls fat mass was derived from studies on Sirt1 overexpressing transgenic mice which showed lower body weight and reduction of fat mass (Bordone *et al.,* 2007) 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 (Chalkiadaki and Guarente, 2012).

One of the key transcription factors regulating adipocyte development is PPARγ which regulates the expression of a number of genes involved in adipocyte differentiation and lipid mobilisation (Tontonoz and Spiegelman, 2008). Acetylation status of lysine residues at position 268 and 293 is critical in the regulation of activity of PPARγ by its co-repressors and activators. Decrease in activity of Sirt1 can affect the acetylation status of these residues on PPARγ. Docking with co-repressors NCoR and SMRT can result in reduction in the transcriptional regulatory activity of PPARγ (Picard *et al.,* 2004). Further, C/EBPα whose activity depends on PPARγ regulated expression of Sirt1 during adipogenesis (Jin *et al.,*

2010). Another possible factor influencing effects of Sirt1 on adipogenesis is the regulation by miRNAs. FOXO1, a protein target of Sirt1, modulates the expression of a number of genes involved in adipogenesis. Mir 146b has been shown to promote adipogenesis by suppressing Sirt1-FOXO1 cascade (Ahn *et al.,* 2013). Sirt2, another member of the sirtuin family of deacetylases which is the predominant one in adipose tissue, has also been shown to suppress adipocyte differentiation by deacetylating FOXO1 and enhancing its repressive interaction with PPARγ (Jing *et al.,* 2007; Wang and Tong, 2009).

In addition to its effect on adipogenesis in WAT, Sirt1 appears to regulate mobilisation of fat. Overexpression of Sirt1 in differentiated 3T3 L1 cells caused decrease in triglyceride levels and increased release of FFAs (Picard *et al.,* 2004). Conversely, knockdown of Sirt1 decreased basal and stimulated lipolysis in adipocytes in culture. Further, activators of Sirt1 such as resveratrol reduced fat mass in high fat diet fed mice (Feige *et al.,* 2008). Likewise, over expression of Sirt1 has been shown to inhibit diet induced accumulation of fat (Bordone *et al.,* 2007; Pfluger *et al.,* 2008). Its effect on fat mobilisation, at least in part, has been shown to be through the modulation of the levels of the rate limiting enzyme adipose triglyceride lipase (ATGL) which is critical in the hydrolysis of triglycerides stored in the lipid droplets in adipocytes. It has been reported that Sirt1 regulates the expression of ATGL gene and thereby lipolysis in adipocytes in culture through modulation of the acetylation and activity of FOXO1 that regulates ATGL gene transcription by directly binding to the ATGL promoter (Chakrabarti *et al.,* 2011). Sirt2 also appears to show similar effect on fat mobilisation indicating redundancy of sirtuins in controlling fat mass (Jing *et al.,* 2007; Wang and Tong, 2009).

Sirtuins Regulate Development and Function of BAT and Browning of WAT

Brown adipose tissue (BAT) is composed of brown adipocytes characterised by multilocular lipid droplets with a central nucleus and a high density of mitochondria (Cannon and Nedergaard, 2004). BAT is essential for classical non-shivering thermogenesis as well as for cold acclimatisation. It is activated whenever extra heat is needed, through a centrally controlled pathway initiated in the hypothalamus and mediated through norepinephrine-β_3 receptor-cAMP-PKA pathway. When BAT is activated, high amount of lipids and glucose are combusted in the tissue (Klingenspore and Fromme, 2012). On stimulation of brown adipocytes, UCP1, a proton transporter, increases the permeability of the mitochondrial membrane causing uncoupling of electron transport chain and dissipation of electrochemical energy as heat resulting in thermogenesis. Sirtuins also appear to play a role in the differentiation and function of BAT. Calorie restriction and cold exposure upregulated the expression of Sirt3 present in the mitochondria in BAT (Shi *et al.,* 2005). Conversely, Sirt3 is down regulated in BAT in mice receiving high fat diet. Sirt1 also appears to have a role in pre-adipocyte differentiation to brown adipocytes as evidenced by the demonstration of Sirt1-related transcriptional signature during brown adipocyte differentiation that may silence myogenic gene expression signature. More specifically, BAT differentiation appears to be influenced by Sirt1 through repression of the MyoD-mediated myogenic gene expression signature and stimulation of PGC-1α mediated mitochondrial gene expression (Timmons *et al.,* 2007). Apart from canonical BAT development, brown remodeling of white fat in response to cold exposure is shown to be regulated by Sirt1-dependent deacetylation of PPARγ. It has been shown that Sirt1-dependent deacetylation of Lys 268 and Lys 293 of PPARγ is required to recruit the BAT programme co-activator Prdm16 to PPARγ leading to selective modulation of expression of BAT genes and repression of WAT genes (Qiang *et al.,* 2012). It is possible that Sirt1 can differentially modulate PPARγ in response to environmental stimuli in WAT. While Sirt1 inhibits PPARγ through local modulation of acetylation status of histones and recruitment of co-repressor NCoR in response to caloric restriction, it directly enhances PPARγ signaling through deacetylation of PPARγ itself during cold exposure (Li, 2013). A recent study using Sirt1 transgenic mice and brown adipocytes derived from them showed that Sirt1 mediated improvement in glucose homeostasis was due to an enhanced response of brown adipocytes to β3-adrenergic stimuli rather than due to differences in differentiation status (Boutant *et al.,* 2015).

Sirt1 is a Key Factor in Obesity and Obesity Related Metabolic Diseases

Excess adipose tissue growth with the concomitant development of blood vessels would result in obesity. Excess consumption of energy leads to adipocytes stress due to increased demand on adipose tissue for

storage of nutrients. Grossly elevated fat stores of the adipose tissue have been associated with the development of dyslipidemia, insulin resistance and hypertension. Sirtuins appear to have a role in obesity and obesity associated pathological conditions. This is suggested by data on the role of sirtuins in adipose tissue development and metabolism, its effects on metabolism of glucose and lipids primarily in the liver, and its effects on pancreas and insulin sensitivity.

Reduced level of expression and activity of Sirt1 in obesity: Association between Sirt1 and obesity has been evident from the decrease in the levels of expression and activity of Sirt1 in adipose tissue in different obesity models. Expression of Sirt1 in adipose tissue of db/db leptin resistant obese mice was significantly low (Qiao and Shao, 2006). Similarly mice fed on high fat diet showed significant decrease in Sirt1 in adipose tissue (Chalkiadaki and Guarente, 2012). Further, as indicated earlier, WAT specific Sirt1 knockout mice showed increased adipogenesis and decreased mobilization of depot fat while the converse was true in Sirt1 over expressed mice (Picard *et al.*, 2004). Transgenic mice over expressing Sirt1 showed decreased levels of plasma cholesterol, insulin and fasting glucose and reduced adiposity (Bordone *et al.*, 2007; Banks *et al.*, 2008). However, another study involving Sirt1 over expression did not show similar effects probably due to variation in the expression levels of Sirt1 (Pfluger *et al.*, 2008), although these animals were protected against the metabolic effects of the diet. Sirt1 over expression in animals on a high fat diet was associated with less inflammation, better glucose tolerance and reduced hepatic steatosis. Sirt1 expression in obese pigs is reported to be lesser than that in lean pigs (Pang *et al.*, 2013). Recently it has been shown that microRNA mir34a,which is elevated in obesity, reduced NAD levels and Sirt1 activity by directly targeting nicotinamide phosphoribosyl transferase (NAMPT) the rate limiting enzyme in the salvage pathway for NAD biosynthesis (Choi *et al.*, 2013).

A possible association of sirtuins with obesity and obesity -associated pathological conditions in humans has been indicated mostly from observational studies. Analysis of Sirt1 mRNA levels in subcutaneous adipose tissue of a small group of women showed an almost two fold higher expression in lean women than obese women (Pedersen *et al.*, 2008). A study on non-diabetic offspring of type 2 diabetic patients showed a positive correlation between Sirt1 mRNA expression in adipose tissue and insulin sensitivity and energy expenditure (Rutanen *et al.*, 2010). Analysis of mRNA and protein levels of Sirt1 in peripheral blood mononuclear cells of diabetic subjects showed lower levels of Sirt1 in subjects with insulin resistance and metabolic syndrome (de Kreuzenberg *et al.*, 2010). Diet induced changes in adipose tissue gene expression were analysed in two groups of obese women who were placed either on a low fat-high carbohydrate diet or a moderate fat –low carbohydrate hypoenergic diet for 10 weeks. Of the nearly one thousand genes regulated by energy restriction, Sirt3 gene expression appeared to be sensitive to hypocaloric diet showing an increased expression during moderate fat intake (Capel *et al.*, 2008). Changes in sirtuins associated with obesity in humans was further evidenced by demonstration of an increase in expression and activity of Sirt1 and Sirt3 in subcutaneous adipose tissue of 29 severely obese patients who experienced weight loss after gastric banding surgery (Moschen *et al.*, 2013). It thus appears that 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. In a large cohort of elderly subjects, two common genetic variants of Sirt1 were shown to be associated with lower BMI; carriers of these variants were assessed to have a 13-18% decreased risk of obesity and gain of less weight over time (Zillikens *et al.*, 2009).

Sirt1 regulates insulin response: Association between Sirt1 expression and insulin sensitivity which is reduced in obese conditions is also evident from both in vitro and in vivo studies. Though Sirt1 is down regulated in insulin resistant cells, induction of Sirt1 expression increased insulin sensitivity of these cells (Banks *et al.*, 2008). Sirt1 regulated insulin-stimulated glucose uptake and GLUT4 translocation in adipocytes; increase in Sirt1 activity attenuated insulin resistance (Yoshizaki *et al.*, 2009). Adipose tissue-specific Sirt1 knockout mice were reported to be more prone to developing insulin resistance. In animals with experimentally induced diabetes, overexpression of Sirt1 increased insulin sensitivity. Sirt1 action apparently involves transcriptional repression of protein tyrosine phosphatase 1B gene which is critical in insulin signaling (Sun *et al.*, 2007). Apart from its effect on insulin target sites modulating insulin

sensitivity, Sirt1 also appears to modulate insulin secretion by β–cells by repressing uncoupler protein 2 (Bordone *et al.,* 2006). While inhibition of Sirt1 expression reduced insulin secretion in β–cell lines, overexpression of Sirt1 increased it. Further, in transgenic mice over expressing Sirt1 in pancreatic β–cells, glucose- stimulated insulin secretion was enhanced (Ramsey *et al.,* 2008). It has also been demonstrated that Sirt1 deficiency impaired insulin secretion by disrupting glucose sensing and impairing response to fluctuations in glucose levels (Luu *et al.,* 2013).

Sirt1 in hypothalamus as a key regulator of central control of energy homeostasis: Apart from its effect on peripheral tissue metabolism, central effects of sirtuins may also be critical. Increase in the expression and activity of Sirt1 has been reported in hypothalamus in both calorie restriction and fasting (Cakir *et al.,* 2009; Satoh *et al.,* 2010). Further, inhibition of hypothalamic Sirt1 expression, specifically in anorexigenic POMC neurons that produce satiety peptides inhibiting food intake after feeding, resulted in loss of response to leptin and reduced energy expenditure indicating that Sirt1 is required in POMC neurons for homeostatic defense against diet- induced obesity (Ramadori *et al.,* 2010). On the other hand, deletion of Sirt1 expression specifically in orexigenic agouti-related protein (AgRP) -expressing neuron which promote feeding in response to fasting, decreased AgRP neuronal activity resulting in decreased food intake and body weight (Dietrich *et al.,* 2010). In a recent study, it has been shown that central inhibition of Sirt1 in rodents on a high fat diet caused decreased body weight and increased energy expenditure 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 (Cyr *et al.,* 2014). It thus appears that Sirt1 has an important central effect in the regulation of nutrient sensing and controlling energy homeostasis.

Sirt1 as a regulator of inflammation in adipose tissue: Excess accumulation of lipids in adipocytes in obesity causes inflammatory events. Accumulation of lipids trigger several intracellular stress pathways including ER stress leading to repression of metabolic pathways and decline in mitochondrial function. Hypertrophic adipocytes, endothelial cells and infiltrated inflammatory cells, particularly macrophages produce various inflammatory markers including TNFα, TGFβ, and several cytokines (Fain *et al.,* 2004; Suganami *et al.,* 2005). Inflammation in adipose tissue is a hall mark of insulin resistance (Shoelson *et al.,* 2006). Inflammation associated with obesity is recognised as a major factor contributing to the pathogenesis of a cluster of diseases associated with metabolic syndrome (Hotamisligil, 2006). There is increasing evidence in support of a role for Sirt1 as a transcriptional regulator of inflammation in multiple tissues, particularly adipose tissue and different types of cells including macrophages and endothelial cells (Yoshizaki *et al.,* 2009; Yoshizaki *et al.,* 2010). While modest over expression of Sirt1 caused suppression of inflammatory response, systemic inflammation was observed in Sirt1 deficient mice on high fat diet (Xu *et al.,* 2010; Purushotham *et al.,* 2012). Adipose specific Sirt1 KO mice displayed increased macrophage recruitment to adipose tissue, while over expression of Sirt1 prevents macrophage accumulation caused by high fat diet (Gillum *et al.,* 2011). A reciprocal relation exists between Sirt1 levels and inflammation in adipose tissue. Sirt1 expression in human subcutaneous adipose tissue was inversely related to macrophage infiltration. The decrease in Sirt1 in obese conditions in adipose tissue is due to the activation of C jun N terminal kinase (JNK1), a key inflammation associated signaling pathway ,which leads to Sirt1 phosphorylation followed by its degradation in proteosomes through a cysteine protease, caspase 1 (Gao *et al.,* 2011; Chalkiadaki and Guarente, 2012).

Several reports suggest that the beneficial effect of Sirt1 on metabolic disorders is partly due to its ability to suppress activation of NFkB, the key transcription factor concerned with the cellular inflammatory response (Kauppinen *et al.,* 2013). Sirt1 has been shown to deacetylate Rel A/p65 subunit of NFkB at Lys 310, decreasing its transcriptional activity thereby reducing production of pro-inflammatory cytokines (Yeung *et al.,* 2004). Consistent with this idea, overexpression of Sirt1 in mice resulted in reduced NFkB activity (Pfluger *et al.,* 2008) while knockdown of Sirt1 increased TNFα secretion in LPS stimulated macrophages (Yoshizaki *et al.,* 2010). Further, the activity and expression of Sirt1 appears to be influenced by systemic inflammation as suggested by repression of transcription of Sirt1 by pro-inflammatory cytokines such as IFNγ (Li *et al.,* 2012). It appears that there is an antagonistic cross talk

between NFkB and Sirt1 signaling in the regulation of inflammation and obesity associated metabolic disorders. While Sirt1 inhibits NFkB signaling directly by deacetylating RelA/p65 subunit, NFkB signaling down regulates Sirt1 activity through the expression of mir34a and IFNγ. It therefore appears 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.

Sirtuin Activators for Therapy

As a decrease in levels and activity of sirtuins is apparently associated with altered metabolic functions in obesity and molecular events in the adipocyte life cycle, activation of Sirt1 is a possible therapeutic strategy. High throughput screening has identified potential Sirt1 activating molecules that increase the affinity of Sirt1 to peptide substrates in in vitro enzyme assay (reviewed in Lavu *et al.,* 2008; Sinclair and Guarente, 2014). Resveratrol, a naturally occurring polyphenol whose antioxidant property and possible benefits thereof have been documented, increased the enzyme activity of Sirt1 (Lagouge *et al.,* 2006). Further, resveratrol and small molecular Sirt1 activators(STACs) have been found to produce significant benefits including improved insulin response, prevention of fatty liver and reduced inflammation in animals fed high fat diet (Milne *et al.,* 2007; Yamazaki *et al.,* 2009). Sirt1 knockdown studies using cells in culture and experimental animals confirmed the requirement of Sirt1 indicating that these compounds exert their beneficial effects through Sirt1 (Feige *et al.*, 2008). Long term intracerebroventricular infusion of resveratrol normalized hyperglycemia and hyperinsulinemia in experimentally induced obese diabetic mice indicating that the small molecular activators of Sirt1 can induce central effects and control diet induced obesity (Ramadori *et al.,* 2009). A few epidemiological studies in humans suggested that resveratrol may provide beneficial effects, although in certain studies no effect was observed (reviewed in Lavu *et al.*, 2008; Sinclair and Guarente, 2013; Tome-Carneiro *et al.*, 2013) probably because of the dose difference and limitation in its bioavailability. Further, the much debated point regarding the validity of the *in vitro* Sirt1 activation by resveratrol was resolved recently by the demonstration of the allosteric site containing a critical E230 residue N-terminal to the conserved domain in Sirt1 and allosteric regulation of its activity by resveratrol and STACs (Hubbard *et al.,* 2013). Several naturally occurring compounds particularly plant polyphenols such as butein, piceatanol, fisetin, quercetin have also been known to activate Sirt1 (Milne *et al.*, 2007). Indole-3-carbinol, which has received attention as a naturally occurring anti-obese agent from brassica vegetables, has been shown to be a potent Sirt1 activator that inhibits adipocyte differentiation (Choi *et al.,* 2013). However its effect on Sirt1 in vivo is yet to be established. Although STACs have been shown to mimic effects of calorie restriction and modulate inflammation and insulin responsiveness, more confirmatory evidence on ameliorating obesity associated complications and /or regulating food intake is required.

CONCLUSION

Remarkable advances in understanding sirtuin biology have been made during the past decade; but many questions remain unanswered, particularly regarding their therapeutic potential in the management of obesity. Apart from functional differences between WAT and BAT, depot dependent variation related to risk for obesity-associated diseases has been reported. It is not clear whether there is any depot dependent variation in sirtuin action. Further, expansion of a highly vascular tissue like adipose tissue is associated with neovascularization. Adipogenesis and angiogenesis are therefore interrelated. Understanding the role of sirtuins in adipose tissue angiogenesis is of paramount importance especially in brown adipose tissue, where both the mitochondrial activity and oxygen demand are high.

ACKNOWLEDGEMENT

M.S is a recipient of the TSS fellowship from the ICMR.

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