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The Emerging Role of Sirtuin 1,-3 and -4 in Glucose and Lipid Metabolism and in Diabetes Mellitus

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Abstract

Diabetes mellitus has been accepted as an epidemic worldwide during the last two decades. Despite the diagnostic tools and therapeutic approaches, the pathophysiology of this metabolic disorder and cellular defensive mechanisms remain mysterious. The maintenance of cellular homeostasis requires well-organized network between glucose, amino acid and lipid metabolism. Sirtuins are a group of nicotinamide adenine dinucleotide dependent proteins that are involved in cellular homeostasis by their deacetylating activity. Among them, sirtuin 1,-3 and -4 have been the most extensively explored. In the present review, we aimed to discuss the role of associated sirtuins in glucose and lipid metabolism and in the pathogenesis and treatment of diabetes mellitus.

Keywords: Sirtuins; Glucose and lipid metabolism; Diabetes mellitus

Introduction

During the last two decades, the prevalence of diabetes mellitus (DM) and its complications have been increasing worldwide despite the diagnostic tools and the therapeutic applications merged into medical practice. Diabetes was both found to be closely associated with cardiovascular morbidity and mortality [1]. Hyperglycemia and related metabolic alterations including advanced glycation end products, polyol, hexosamine and protein kinase C pathways collectively contribute the classical pathogenesis of diabetes. However, there are conflicting results regarding the role of vigorous serum glucose control on major cardiovascular events [2,3]. The main reasons for these undesirable consequences of diabetes might be secondary to unlighted pathophysiological mechanisms. To date, novel risk factors including increased inflammatory cytokines secondary to low grade persistent inflammation, adipose tissue hormones (adipokines) including obestatin, leptin, resistin and renin-angiotensin-aldosteron system are determined as the most detrimental factors attributed to this heightened cardiovascular morbidity and mortality in diabetic and obese patients [4]. It is unlogical to treat these various entities separately. Therefore, the main source of the detrimental pathogenetic mechanisms should be determined and new therapeutic molecules should be identified to accomplish the treatment of diabetes.

In this regard, two questions should be arised. First, what is the main defensive mechanism against these undesirable pathophysiologic events responsible for increased cardiovascular morbidity and mortality? Second, are there any novel treatment modalities that include the mechanisms to overcome these worse outcomes?

Sirtuins are a group of proteins that have an enormous capacity to deacetylate various enzymes and proteins within the cell. Activation or deactivation of the enzymes occurs as a consequence of this deacetylation. Since both carbohydrate and lipid metabolism are affected in diabetes, perhaps sirtuins are the responsible key proteins that fights against the detrimental effects of these disorders and may be the main answer of these two important questions. In the literature, the biological mechanisms of sirtuins were extensively discussed [5] and except SIRT 1,-3 and-4, effects of other sirtuins are the beyond the scope of this review. Hence, we will focus on the mechanisms of sirtuins in carbohydrate and lipid metabolism regarding diabetes mellitus in the present review.

Overview of Sirtuins

Mammalian sirtuins are a group of proteins that consist of seven nicotinamide adenine dinucleotide (NAD^+) dependent enzymes (SIRT1 through SIRT 7) with homology to Sir 2 (silent information regulator 2) family of Saccharomyces cerevisae [6]. The main function of these enzymes is to deacetylate the various proteins that regulate a wide variety of cellular processes regarding protein, carbohydrate and lipid metabolism, mitochondrial homeostasis and programmed cell death mechanisms including autophagy and apoptosis [7]. Among them, SIRT 4 and-6 have an additional ADP-ribosyltransferase activity that is also important in telomere maintenance, genomic stability and longevity [8,9]. Sirtuins remove the acetyl groups from lysine residues of histones, transcription factors specific enzymes such as manganese superoxide dismutase and peroxisome proliferator activated receptor–γ (PPR-γ) -coactivator-1α (PGC-1α) and other miscellaneous proteins that have important roles in the cellular homeostasis [10]. As a consequence of the deacetylation, nicotinamide and 2'O-acetyl-ADP ribose are generated [11].

Recent studies demonstrated that sirtuins can be found and activated in kidney, liver, spleen, lung, heart, pancreas, muscle, brain, testis, ovary, thymus, white and brown adipose tissue [12]. In the cell, the localization of SIRT proteins differ and matter, hence, the different localizations develop various physiologic and may be pathologic metabolic effects under certain stress conditions. The first two SIRT proteins, SIRT 1 resides both in the nucleus and cytoplasm and SIRT 2 is primarily found in the cytoplasm, however, it can be transferred into the nucleus in a cell cycle-dependent manner. SIRT 3,-4 and-5 exist in the mitochondria. The last two members of SIRT protein family, SIRT 6 and-7 are found in the nucleus and the nucleolus of the cell, respectively [13].

How can Sirtuins be Activated in the Cell?

Previous experimental studies showed the beneficial effects of decreasing food intake by 30% without malnutrition, also named Calorie Restriction (CR) on aging that could be mediated by sirtuin over expression and this effect leads to increasing lifespan [14]. Basically, increased intracellular NAD^+ concentrations and CR are the main factors that activate sirtuins. In energy rich conditions, NAD^+ is reduced to Nicotinamide Adenine Dinucleotide (NADH) and the proportion of NAD^+ to NADH is reduced during glycolysis, cyclic acid cycling, lipid β-oxidation and protein catabolism [15]. Two main sources of NAD^+ are salvage pathway of nicotinamid catalyzed by enzyme named nicotinamidphosphorybosyltransferase (NAMPT) and de novo synthesis from tryptophan metabolism [16].

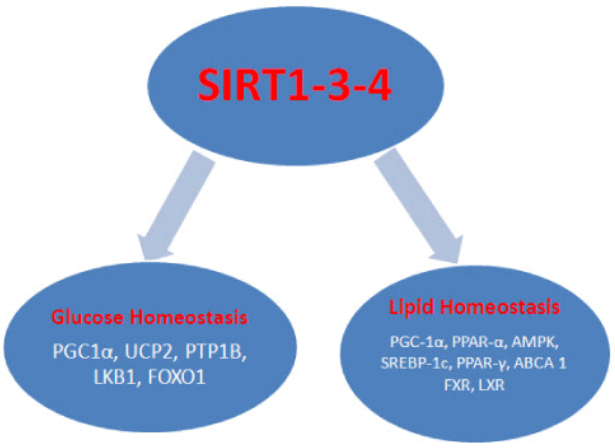

Figure 1: The transcription factors that are affected by SIRT1, 3 and 4

Among others, SIRT 1 is the most studied member of sirtuins probably because of the generalized effects on the cell cycle, mitochondria metabolism, energy homeostasis, inflammation, oxidative stress and apoptosis [17]. SIRT 1 can directly deacetylate nuclear histone proteins that results in repression of gene transcription [18]. On the other hand, metabolic effects of SIRT 1 depend on the deacetylation of non-histone proteins including PGC-1α, insulin receptor substrate (IRS)-2, peroxisome proliferator activated receptor (PPAR)-α, PPAR-γ, mitochondrial uncoupling protein 2 (UCP-2), liver X receptor (LXR), farnesoid X receptor (FXR) and sterol-regulatory-element binding protein (SREBP) [19-23]. In this regard, SIRT 1 regulates insulin secretion, adipogenesis and myogenesis. The transcription factors that are affected by SIRT1, 3 and 4 are shown in Figure 1. Deacetylation of transcription factors including PGC1α, UCP2, PTP1B, LKB1 and FOXO1 by SIRT1,-3,-4 upregulate the genes of enzymes that are closely related to glucose metabolism. On the other hand, the same sirtuins are involved in the activation of PGC-1α, PPAR-α, AMPK, SREBP-1c, PPAR-γ, ABCA 1 FXR, LXR which are related to lipid metabolism. These mechanisms will be detailed in the following sections of this review.

The Role of Sirtuins in Glucose Metabolism

Glucose metabolism is regulated by hormones including insulin, glucagon, growth hormone and adrenalin. In normal physiology, insulin is released from pancreatic islet β cells when glucose enters the circulation after a meal. Insulin removes glucose from plasma and promotes cellular uptake in skeletal muscle and adipose tissue via insulin receptors which are closely related with a protein named insulin receptor substrate-1 (IRS-1). IRS-1 is an intracellular protein which is tyrosine phosphorylated that confers the ability to bind another set of intracellular signaling proteins which contains the SH2 domain. It has been thought that IRS-1 is a sort of docking protein for the SH2-containing signaling proteins. The downstream pathways of IRS1 are phosphatidylinositol-3-kinase/Akt pathway that regulates glucose transporter type 4 translocation and mitogen activated protein kinase (MAPK/ERK) pathway which mediates the cell growth and differentiation [24]. In this regard, after uptake of glucose into the cells, insulin promotes the conversion of glucose to glycogen and lipids in fed state (Figure 2). The effects of insulin differ according to the cell type. Insulin activates glycogen synthase and deactivates hepatic phosphorylase via its dephosphorylation activity. In liver, insulin induces glycogen synthesis through phosphorylation of glucose via a couple of enzymes including glucokinase and glycogen synthetase. Glycogen within the hepatocyte is a major source of stored carbohydrate. Glycogen is also stored in the skeletal muscle and other cells in smaller amounts. Additionally, insulin stimulates the conversion of free fatty acids into triglycerides that means lipid synthesis also occurs in the liver. During fasting, hepatic glucose output is increased secondary to the activation of gluconeogenesis and the inhibition of glycolysis. Sirtuins, especially SIRT1, influence many steps of glucose metabolism in liver, pancreas, muscle and adipose tissue (Figure 3). The main regulator of these reactions is deactylated form of PGC-1α in SIRT 1 activated states [25].

Forkhead box group O (FOXO), a group of transcriptional factors, has been found to be very effective in terms of sensing nutrient deprivation and promoting cellular homeostasis [26]. Among them, FOXO 1 regulates glucose metabolism [27] and feeding behaviors [28]. In normal physiology, during fasting state, the balance between insulin and glucagon (decreased insulin versus increased glucagon) stimulates gluconeogenesis via cAMP-Responsive Element Binding protein (CREB) regulated transcription coactivator 2 (CRTC2) and FOXO1 [29,30].

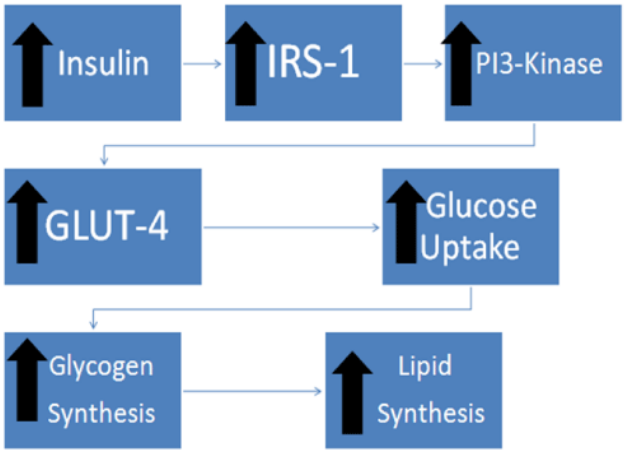

Figure 2: Metabolic Effects of SIRT1 in Peripheral Organs

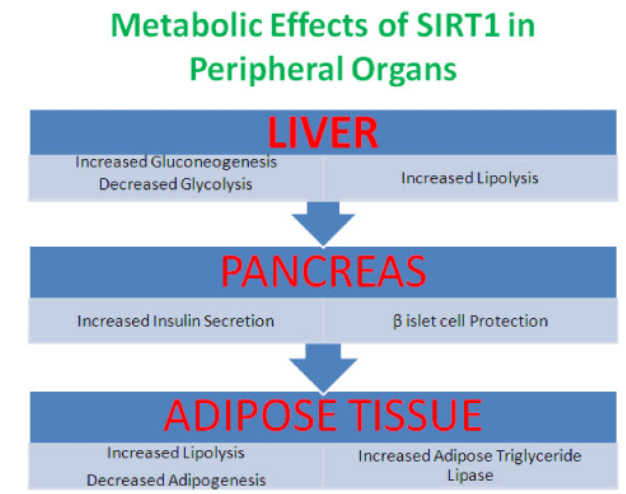

Figure 3: Metabolic Effects of Insulin in Cells

Recently, the link between FOXO proteins, STAT 3 (Signal transducer and activator of transcription 3) and SIRT 1 regarding hepatic glucose metabolism is identified. Both FOXO1,-3a,-4 were found to be associated with increased expression of gluconeogenesis genes and decreased expression of glucokinase [31,32]. SIRT 1 also regulates gluconeogenesis via deacetylation and thereby deactivating STAT 3 which can inhibit the transcription of gluconeogenic genes in normal conditions [33].

The role of sirtuins in the pancreas was demonstrated. Experimental data of SIRT 1 over expression suggested that serum insulin and cholesterol were diminished along with the diminution of the adipose tissue volume and decreased obesity-induced insulin resistance [34,35]. Interestingly, SIRT 1 deficient mice also exhibit low levels of serum glucose and insulin [36]. Despite the repetitive results of the studies regarding the calorie restriction (CR) induced SIRT 1 expression, Moynihan et al. [23] firstly demonstrated that β-cell-specific SIRT 1 transgenic mice exhibit insulin secretion *ex vivo* in pancreatic β islet cells in response to high glucose. This result was confirmed by Bordone et al. [36] who also pointed out that insulin secretion was reduced in SIRT1 knock-out mice and in pancreatic β islet cell lines in which SIRT1 had been knocked down by RNA interference. This effect partially depends on the SIRT 1-mediated inhibition of uncoupling protein-2 (UCP-2) in pancreatic islet β-cells [23]. UCP-2 is a mitochondrial inner membrane that regulates mitochondrial ATP synthesis. SIRT1 knock out mice exhibit increased UCP-2 in β-cells along with low levels of serum insulin [36] and higher pancreatic secretion of insulin and ATP were demonstrated in UCP-2 knock out mice [37]. According to these study results, SIRT 1 might be a positive regulator rather than a suppressor of insulin in the postprandial fed state.

Insulin sensitivity is considered as an important part of the glucose metabolism. Protein tyrosine phosphatase 1B (PTP1B) is involved in glucose metabolism and diet-induced obesity [38]. SIRT 1 represses PTP1B by deacetylation which is a tyrosine phosphatase for the insulin receptor. In accordance, resveratrol, an activator of SIRT1 may also inhibit PTP1B. Hence, SIRT 1 might improve insulin sensitivity in insulin-resistant conditions via reducing PTPB1B activity [39].

SIRT 3, a mitochondria localized sirtuin, have also beneficial effects on glucose metabolism by increasing insulin sensitivity and decreasing serum glucose. Hirschey et al. [40] recently demonstrated that high-fat diet feeding induces hepatic mitochondrial protein hyperacetylation in mice and down regulation of the major mitochondrial protein deacetylase SIRT3. According to the results of this study, increased obesity, insulin resistance, hyperlipidemia, and steatohepatitis are prominent in mice lacking SIRT3 compared to wild-type mice [40]. The same group also identified a single nucleotide polymorphism which encodes a point mutation in the SIRT 3 protein. As a result, mitochondrial protein acetylation is impaired and polymorphism of SIRT3 has been shown to associate with the metabolic syndrome [40].

Another important sirtuin that takes part in glucose metabolism is SIRT4. In contrast to SIRT1, both the localization and the function of SIRT4 are different. SIRT4 is located in mitochondria and transferases ADP-ribose to the substrates. One of the target enzyme of SIRT4 is glutamate dehydrogenase (GDH) which converts glutamate to α-ketoglutarate in the mitochondria [41]. SIRT4 inhibits amino-acid induced insulin secretion via repressing GDH [42]. During fasting, SIRT4 is found to be inhibited in liver to induce glucogenesis from amino acids and fats and in the mean time inhibition of SIRT4 allows insulin secretion from β-cells. However, SIRT4 is activated and the reactions mentioned above are reversed in fed states [41].

The Role of Sirtuins in Lipid Metabolism

In fat tissue, approximately 90% of stored glucose is found in the form of lipids primarily as triglycerides. In adipocytes, insulin activates lipoprotein lipase, hence, insulin actively take place in the fat tissue. Recent advances highlightened the roles of sirtuins, especially SIRT 1 and SIRT 3, in the pathogenesis of adipogenesis. The most studied transcription factors that have an important roles in the adipogenesis and lipid synthesis are PGC-1α, PPAR-α, AMPK (adenosine monophosphate–activated protein kinase), LKB1 (liver kinase B1), SREBP-1c, PPAR-γ, ABCA 1 (ATP-binding cassette transporter 1), FXR, LXR-α and LXR-β [10]. Deacetylation of PGC-1α by SIRT 1, which is highly expressed from the liver in the starved state and vice versa, results in increased hepatic glucose output via increasing hepatic gluconeogenesis and inhibiting glycolysis [43]. In addition, SIRT 1

activates PPAR-α secondary to PG-1α deacetylation, which is very important in fatty acid β oxidation in the liver, striated and smooth muscles [20]. SIRT 1 also stimulates LKB1 and AMPK that enhances fatty acid β oxidation in the liver [44]. In contrast, SIRT 1 inhibits SREBP 1 and this inhibition results in increased lipolysis in the liver [19].

PPAR- γ, one of the regulator of adipogenesis, is also inactivated by SIRT 1. In this regard, inhibition of PPAR-γ causes diminished adipogenesis therefore obesity, and increases free fatty acid release in white adipose tissue [45] (Figure 2).

Another regulatory function of SIRT 1 is cholesterol biosynthesis. LXR-α and LXR-β are two important nuclear proteins that maintain and control synthesis of cholesterol. These proteins stimulate the activation of ABCA-1 that results in high density lipoprotein (HDL) synthesis. Hence, Li et al. [46] concluded that deacetylation of LXR proteins might be associated with the pathogenesis of atherosclerosis especially in chronic metabolic disorders including diabetes.

Farnesoid X receptor , also known as bile acid receptor, is another member of nuclear receptor family, was found to be closely related with glucose and lipid metabolism. Deacetylation of FXR by SIRT 1 represses the activation this protein, therefore the deleterious metabolic effects were inhibited [47].

In fasting state, one of the main energy source is free fatty acids. SIRT1 induces PGC1-α and PPAR-α that result in increased mitochondrial free fatty acid oxidation [20]. In addition, SIRT1 knock out mice exhibit hepatosteatosis secondary to accumulation of fats in the liver [48]. SIRT3 is also involved in the pathogenesis of hepatic lipid metabolism by deacetylating and activating long chain acyl CoA dehydrogenase [49]. In contrast, SIRT4 has opposite effects on free fatty acid metabolism and induction of SIRT4 might increase hepatosteatosis [50].

The Role of Sirtuins in Type 2 Diabetes Mellitus

In the early stages of Type 2 DM, insulin resistance is the prominent feature and as a result hyperinsulinemia occurs. Impaired glucose uptake and utilization follow this stage and hyperglycemia and hyperinsulinemia contribute the pancreatic β islet cell destruction with the progression of diabetes [51].

As mentioned above, by deacetylating FOXO1 and PGC1α, SIRT 1 induces gluconeogenesis and inhibits glycolysis in liver during fasting. What about the changes of both gluconeogenesis and glycolysis in diabetes mellitus? Rodgers and Puigserver [52] showed that hepatic PGC1α is up regulated and gluconeogenesis is also increased which can further aggravate hyperglycemia in diabetic mice. In type 1 diabetes mellitus model of mice, Yechoor et al demonstrated that SIRT3 mRNA is down-regulated [53]. In another study done by Hallows et al explored that SIRT3 induces the ketogenesis by activating acetyl-coA synthetase in the mammalian cells [54]. Hence, one might expect that SIRT3 might play an important role for the increased ketogenesis observed during diabetes.

Hepatosteatosis is commonly seen in diabetic patients. As mention above, SIRT1,-3 and -4 play an important role in the pathogenesis of this entity [50]. When taken together, inhibition of SIRT1 and 3 and/or activation of SIRT4 might be attributed to this heightened risk of hepatosteatosis in the progression of diabetes.

Novel Therapeutic Agents of SIRT1 Activators in Treatment of Diabetes Mellitus

The first actor that suggested to activate SIRT 1 was a plant polyphenol, resveratrol (trans-3,5,4'-trihydroxystilbene). This molecule is mostly found in peanuts and grapes. Resveratrol might attenuate chronic inflammation which is an important part of the pathogenesis of diabetes and obesity. In the first studies, the beneficial metabolic effects of resveratrol was attributed to SIRT1 activation [55]. However, in the following years, it was demonstrated that the positive effects of resveratrol on glucose metabolism and insulin sensitivity is closely associated with AMPK subunit α activation of this agent rather than the stimulatory effect on SIRT 1. In this regard, Um et al. [56] demonstrated that resveratrol could not improve glucose tolerance and insulin sensitivity in AMPK α knockout mice. Treatment with resveratrol, reduced macrophage infiltration, insulin resistance, hepatosteatosis and serum levels of tumor necrosis factor-α in high-fat diet fed mice [57]. In a human study, recently, Timmers et al. [58] showed the beneficial effects of resveratrol in obese patients in terms of lowering systolic blood pressure, serum lipid and glucose levels and inflammation parameters.

There are conflicting results regarding the effects of novel synthetic SIRT1 activators on glucose and lipid metabolism. Yamazaki et al. [59] showed that treatment of mice with nonalcoholic fatty liver disease with a synthetic SIRT1 activator, SRT1720, might decrease the serum lipid levels, oxidative stress and inflammation. In addition, Feig et al. [60] showed that activation of SIRT1 by SRT1720 protected the organism from diet-induced insulin resistance and obesity via increasing oxidation of fat in liver, adipose tissue and skeletal muscle. However, some studies suggested that SIRT1 overexpression might have adverse effects on lipid metabolism and may be associated with increased lipogenesis [61,62]. In this regard, Caton et al. [63] demonstrated that fructose induced gluconeogenesis, with increases in peroxisome proliferator-activated receptor coactivator 1-alpha and phosphoenolpyruvatecarboxykinase (PEPCK) gene expression, PEPCK activity, and hepatocyte glucose production. In addition, levels of 3-hydroxy-3-methylglutaryl coenzyme A reductase and intracellular cholesterol were increased. Increases in gluconeogenesis, HMG Co-A reductase and cholesterol were abolished by SIRT1 inhibitors, while SIRT1 activator, SRT1720, increased gluconeogenesis and lipogenesis via increased HMG Co-A reductase gene expression [63]. Finally, studies defining the exact role of SIRT1 on lipid metabolism are needed.

Nicotinamid mononucleotide (NMN), a NAD^+ intermediate, is another attempted molecule that has been demonstrated to have beneficial effects as improved glucose and lipid levels in aging-induced diabetes. In the experimental model of high-fat induced diabetic mice, intraperitoneal injection of NMN in 500 mg/kg/day doses in 5-7 days, has been found to be associated with better serum glucose and insulin levels [64]. This study suggested that an increase in NAD via NMN might improve metabolic parameters in diabetic patients.

Niacin, (vitamin B3) is also an important intermediate for the biosynthesis of NAD^+ that can used for the activation of SIRT1 [65]. Niacin is essential to all living organisms and biosynthetically converted to NAD within the cell. NAD plays a vital role in maintaining the genome stability via sirtuins [66]. Hence, it would be logical to consider niacin as a therapeutic agent to activate SIRT1. Metformin, a commonly used anti-diabetic drug, decrease insulin resistance and hyperglycemia via inhibiting gluconeogenesis, hepatic

glucose output and activation of free fatty acid oxidation in skeletal muscle [67]. Some of these beneficial effects of metformin were attributed to SIRT1 activation via AMPK pathway [68].

Calorie restriction provides a desirable metabolic profile and improvement of the mitochondrial functions in humans via activating several genes including SIRT1 [69]. In this regard, CR with increased physical activity should be encouraged especially in obese diabetic patients.

SIRT1 activators might induce insulin secretion and sensitivity, reduce adipogenesis, but also induce gluconeogenesis in the liver, which may worsen hyperglycemia in diabetic. Hence, among the mentioned treatment options, except metformin and CR, none of them is used in large series of clinical trials. To date, therefore, it is wise to use only metformin along with CR in obese type 2 diabetic patients to get beneficial metabolic effects.

Conclusion and Future Perspectives

As a conclusion, certain cellular stresses, CR, oxidative stress, and various endogenous proteins and so forth might decrease nicotinamid and increase NAD/NADH ratio that trigger sirtuins. In fasting state, sirtuins inhibit insulin release in the pancreas and prevent β-cell degeneration, promote gluconeogenesis and insulin signaling, inhibit glycolysis and adipose differentiation, and prevent ketogenesis especially in diabetes (Figure 4). Hence, activation of sirtuins result in various beneficial metabolic effects which makes these proteins a target new drugs especially for the future treatment of metabolic disorders including diabetes and obesity. However, there are many missing pieces in the puzzle and further experimental and clinical studies are needed to highlight the roles of sirtuins in diabetes mellitus.

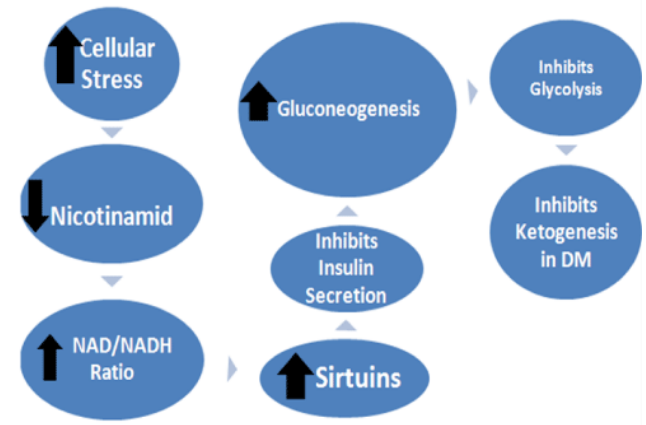

Figure 4: Explanatory diagram of Response to Cellular Stress

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