SIRT1 and metabolic syndrome

SIRT1 i zespół metaboliczny

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Summary

Both obesity and type 2 diabetes mellitus, two major components of metabolic syndrome, become health epidemics in the world. Over the past decade, advances in understanding the role of some regulators participating in lipid and carbohydrate homeostasis have been made.

Of them, SIRT1, the mammalian orthologue of the yeast Sir2 protein has been identified. SIRT1 is a nuclear NAD^+-dependent deacetylase that targets many transcriptional modulators, including PPAR-α and -γ (peroxisome proliferator-activated receptors α and γ), PGC-1α (PPAR-γ coactivator-1α), FOXO (forkhead box O proteins), and nuclear factor κB (NF-κB), thereby this enzyme mediates a wide range of physiological processes like apoptosis, fat metabolism, glucose homeostasis, and neurodegeneration.

In this article, we discuss how SIRT1 regulates lipid and carbohydrate metabolism, and insulin secretion in different metabolic organs/tissue, including liver, muscle, pancreas, and fat. Additionally, the role of this enzyme in reduction of inflammatory signalling is highlighted.

Key words: metabolic syndrome, diabetes mellitus type 2, obesity, SIRT1.

Streszczenie

Dwa główne elementy syndromu metabolicznego – otyłość oraz cukrzyca typu 2 – stały się światowym problemem epidemiologicznym. W ostatnich latach nastąpił duży postęp w rozumieniu roli niektórych regulatorów homeostazy lipidowo-węglowodanowej. Wśród nich został zidentyfikowany występujący u ssaków ortolog drożdżowego białka Sir2 – SIRT1. Należy on do jądrowych NAD^+ zależnych deacetylaz. Deacetyluje wiele czynników transkrypcyjnych, w tym PPARα i γ (receptor aktywowany przez proliferatory peroksysomów α i γ), PGC-1α (PPAR-γ koaktywator-1α), FoxO (białko forkhead box O) oraz czynnik jądrowy κB (NF-κB), tym samym pośredniczy w dużym spektrum fizjologicznych procesów, takich jak apoptoza, metabolizm tłuszczy, homeostaza glukozy oraz neurodegeneracja.

W niniejszym artykule przedstawiono wpływ SIRT1 na regulację wydzielania insuliny oraz regulację metabolizmu węglowodanowo-lipidowego w różnych organach/tkankach, w tym w wątrobie, mięśniach szkieletowych, trzustce oraz tkance tłuszczowej. Dodatkowo zwrócono uwagę na rolę tego enzymu w redukcji stanów zapalnych.

Słowa kluczowe: zespół metaboliczny, cukrzyca typu 2, otyłość, SIRT1.

Introduction

Insulin resistance and obesity are believed to be significant factors of metabolic syndrome, a complex disorder that involves metabolic, hormonal, genetic, and lifestyle interactions, which contribute to the development of type 2 diabetes (T2DM), one of the leading chronic metabolic diseases worldwide resulting in both morbidity and mortality. The World Health Organization estimates that the number of people with diabetes in the world will rise from 171 million in 2000 to 366 million in 2030 [1]. Taking into account that the pathogenesis of T2DM is very complex and characterized by insulin resistance in peripheral tissues (i.e. the liver,

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skeletal muscle, and adipose tissue) and the pancreatic beta cell dysfunction causing decreased insulin secretion [2], many studies have focused on identifying molecular targets which might lead to improvement in tissue insulin sensitivity. In recent years, much evidence has supported the prominent role played by sirtuins, especially SIRT1, in regulation of glucose homeostasis [3], insulin secretion [4, 5], and lipid mobilization [6]. Therefore, the goal of this review is to demonstrate recent advances in understanding the role of SIRT1 in the control of metabolic homeostasis, particularly in lipid and carbohydrate metabolism, with a special consideration of its potential therapeutic significance in the treatment of metabolic diseases, such as obesity and T2DM.

General characteristics of sirtuins

The sirtuin (Silent information regulator, Sir2) proteins belong to the NAD^+-dependent deacetylases which are present in both prokaryotes and eukaryotes. In yeast, Sir2-mediated deacetylation of histones was shown to repress transcription of mating-type loci (*HML* and *HMR*), telomeres, and ribosomal DNA, thereby these enzymes are believed to be essential transcriptional silencers in yeast [7]. Another important role of Sir2 in lower organisms such as yeast (*Saccharomyces cerevisiae*) and/or worms (*Caenorhabditis elegans*), is their ability to extend life span [8].

In humans, seven diverse sirtuins (SIRTs), denoted as SIRT1-7, have been identified so far, with their differentiated intracellular localization: both SIRT1 and SIRT6 were found in nucleus, SIRT2 in cytosol, SIRT3-5 in mitochondria, and SIRT7 in nucleolus [9]. Among them, SIRT1, 2, 3, 6 and probably 5 are NAD-dependent deacetylases, whereas SIRT4 and 6 are ADP-ribosyltransferases which transfer the ADP-ribosyl moiety from NAD^+ to the protein substrate leading to their inhibition. In the case of SIRT7, its catalytic activity has not yet been clarified [10].

SIRT1, being the closest human homolog of the yeast Sir2, has been well characterized in mammals with respect to its substrates, the mechanism of substrate deacetylation, and some physiological functions. It has been established that SIRT1 deacetylates a wide range of non-histone proteins which are key transcription factors or cofactors, such as p53, Ku70, FOXO (forkhead) proteins, TAF_I68, MyoD, NF-κB (nuclear factor κB), PPAR-γ (peroxisome proliferator-activated receptor-γ), PGC-1α (PPAR-γ coactivator-1α), thereby it widely contributes to regulation of apoptosis, cell cycle, transcriptional silencing, fat mobilization, aging, and regulation of insulin pathway [9]. The mechanism of SIRT1-mediated deacetylation of the above-mentioned substrates includes binding of protein with acetylated lysine (the first substrate) and β-NAD^+ (the second substrate) to the enzyme and, in a subsequent step, cleavage of the high energy glycosidic bond between the ADP-ribose moiety and nicotinamide (NAM) in NAD^+ resulting in the release of three final products like *O*-acetyl-ADP-ribose (the mixture of 2' and 3'-*O*-acetyl-ADP-ribose), NAM and the protein substrate with deacetylated lysine moiety (Fig. 1) [11]. It should be noted that NAM suppresses deacetylation by inducing a reverse reaction. Additionally, several specific SIRT inhibitors other than NAM, such as splitomicin, sirtinol, cambinol, were identified and tested in biological systems as novel potential therapeutic agents (Fig. 1) [12].

Sirtuin activating compounds (STACs)

Recent studies are focused on a search for STACs which can be valuable tools to investigate the regulatory role of sirtuins in various types of cells and to potentially use these compounds for the treatment of metabolic disorders such as obesity or diabetes. To date, the most acclaimed natural activator of SIRT1 is resveratrol, a natural polyphenol present in the skin of grapes and red wine, which was found to extend the life span of *S. cerevisiae, C. elegans,* and *D. melanogaster* in a Sirt1-dependent manner [13]. In mammals, Bauer *et al*. [14] characterize the consequences of resveratrol treatment of mice on a high-calorie diet, by showing that these animals have extended life span resulting from increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-1) levels, increased AMP-activated protein kinase (AMPK) and PGC-1α activity, increased mitochondrial number, and improved motor function. Additionally, in a rat model for type 1/type 2 diabetes resveratrol not only reduced diabetes symptoms but also significantly decreased insulin secretion and delayed the onset of insulin resistance [15]. Besides resveratrol, novel small-molecule selective activators of SIRT1, structurally unrelated to resveratrol, have been synthesized and investigated in diet-induced obese and genetically obese mice [16, 17]. Among them, SRT1720, eliciting the 1000-fold increase of SIRT1 enzymatic activity compared to resveratrol, has been shown to improve glucose and insulin homeostasis, increase insulin sensitivity in liver, skeletal muscles, and fat tissue as well as to enhance mitochondrial function in rodent models of T2DM [16]. These results are consistent with the role of SIRT1 downstream of calorie restriction and, moreover, they support the hypothesis that SIRT1 activation *in vivo* by small molecules mimics calorie restriction [17]. In contrast to the above-described data, the most recent study by Pacholec *et al*. [18] has revealed that neither SRT1720 nor resveratrol are direct SIRT1 activators and they interact with multiple unrelated targets, suggesting that these compounds would not serve as useful pharmacological tools for studying SIRT1 pathways. Regarding SRT1720, no decrease in plasma glucose was observed after treating high-fat-fed obese mice with this compound. Given the

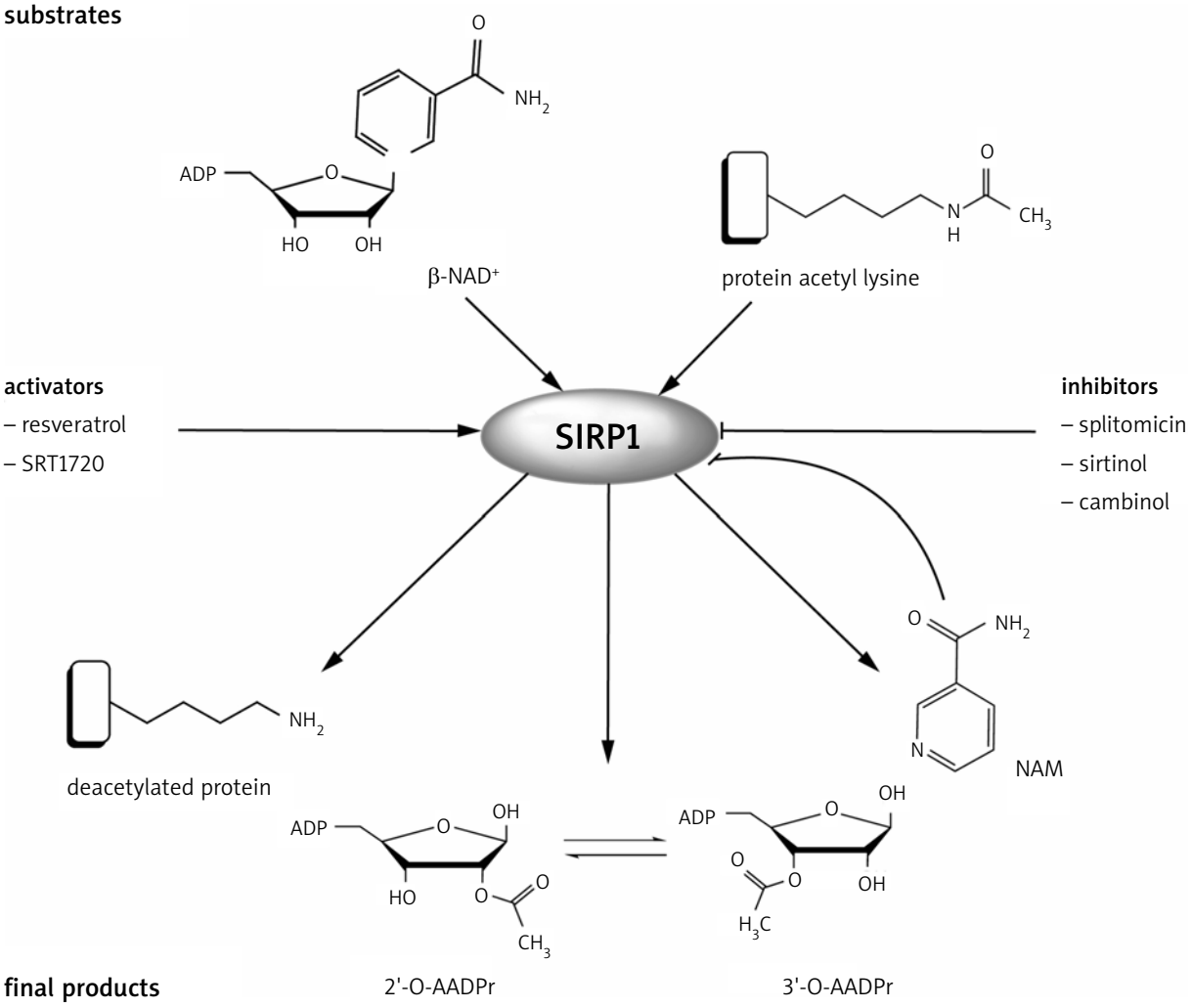

Fig. 1. SIRT1-mediated deacetylation of proteins and modulators (activators and inhibitors) in this reaction

above, more studies are needed to establish whether resveratrol acts directly or indirectly on SIRT1 since this polyphenol is routinely utilized to activate SIRT1 in various cell cultures and animal models.

Sites of SIRT1 activity

In this section, we summarize the role of SIRT1 in the maintenance of glucose and lipid homeostasis in different metabolic tissues, including liver, fat, pancreas, and muscle. A schematic overview of how SIRT1 affects tissue-specific metabolic pathways, depending on the specific factors involved, is presented in Fig. 2.

Liver

Liver is the major organ responsible for synthesis, storage, and consumption of glucose and lipids, thus, it plays an essential role in the maintenance of glucose and lipid homeostasis under physiological conditions. Several lines evidence indicates that hepatic SIRT1 is an important factor in the regulation of glucose and lipid metabolism in response to fasting [3, 19]. Indeed, it has been shown that in the fasted state, SIRT1 interacts with and deacetylates a nuclear receptor coactivator PGC-1α, thereby PGC-1α suppresses glycolysis, induces both gluconeogenic gene expression (phosphoenolpyruvate carboxykinase, PEPCK; glucose-6 phosphatase, G6Pase) and hepatic glucose output [3] as well as it affects expression of fatty acid oxidation and triglyceride genes [19]. Moreover, fasting increases NAD^+ and SIRT1 levels in mouse liver indicating that SIRT1 is a sensor for nutrient fluctuations through the NAD^+ control [3]. Additionally, the SIRT1-mediated deacetylation of PGC-1α may promote transcription of PPAR-α and, consequently, induce expression of fatty acid catabolic genes [20]. Another substrate for SIRT1 is the nuclear factor FOXO1 that in its deacetylated form is able to promote some

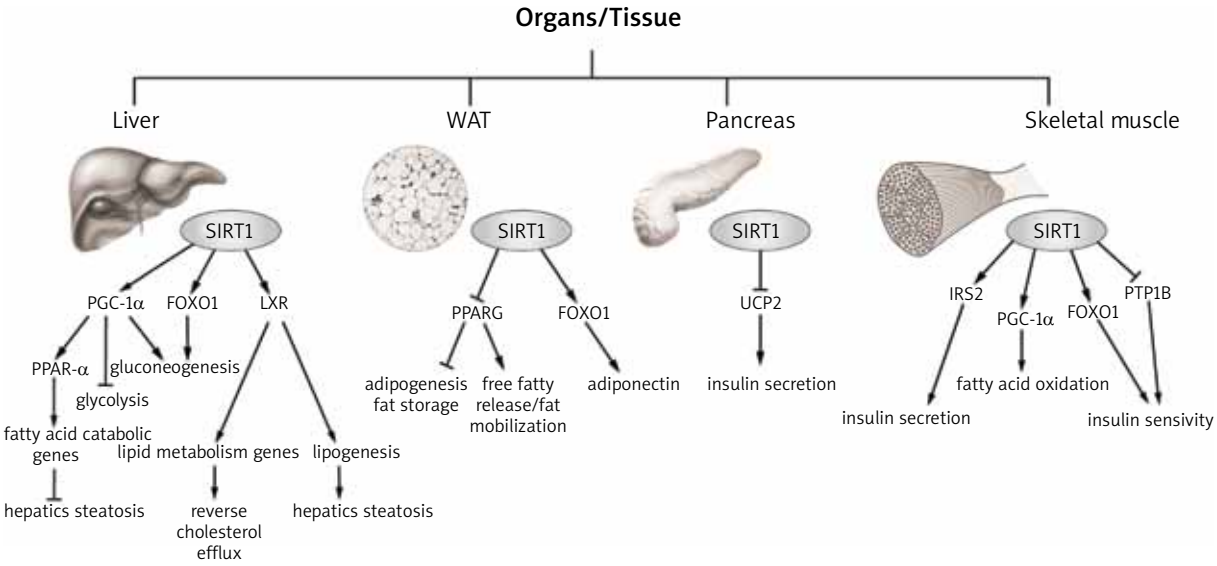

Fig. 2. Schematic representation of SIRT1 action in the liver, WAT, pancreas, and skeletal muscle. Activation → Inhibition ⊣

gluconeogenic genes [21]. Recently, SIRT1 was found as a positive regulator of the liver X receptors (LXRs) α and β, two ligand-activated transcription factors belonging to the nuclear receptor superfamily, which control cholesterol homeostasis through a regulation of reverse cholesterol transport (RCT), i.e. the transport of excess cholesterol on high-density lipoprotein (HDL) particles from peripheral tissues to the liver [22]. Li *et al.* [22] showed that SIRT1 promotes the transcription of LXR target genes involved in lipid metabolism and RCT, thereby this enzyme may be a mechanism that affects atherosclerosis and other aging-associated diseases. Most recently, studies concerning the role of SIRT1 in regulation of fatty acid homeostasis in the liver have revealed that SIRT1 heterozygous knockout [SIRT1(+/–)] mice on high-fat diet exhibited a significant increase in hepatic steatosis. Thus, these findings may imply that a reduction in the SIRT1 activity increases the risk of liver steatosis in response to dietary fat, apparently, as a result of increased lipogenesis and reduced liver fat export [23]. However, the precise molecular mechanism by which SIRT1 can affect fatty liver remains to be established.

White adipose tissue

Human white adipose tissue (WAT), besides lipid storage, plays an important role as an endocrine organ producing a large number of hormones and cytokines involved in the development of metabolic syndrome, diabetes mellitus, and vascular diseases. In WAT, there are two main transcriptional factors like PPAR-γ, that activate genes involved in adipocyte differentiation and fatty acid trapping (e.g. fatty acid transport protein, LPL, fatty acid-binding protein, adiponectin, and acyl-CoA synthase) [24], and SREBP-1c (sterol regulatory element-binding protein 1c), that participates in activation of genes required for endogenous lipogenesis and pre-adipocyte differentiation (e.g. fatty acid synthase, HMG-CoA synthase) [25]. SIRT1 has been shown to interact with PPAR-γ and suppress its activity through docking with PPAR-γ cofactors [i.e. nuclear receptor co-repressor (NCoR) and the silencing mediator of retinoid and thyroid receptors (SMRT)], leading to the down-regulation of genes mediating adipogenesis and fat storage [6]. In fully differentiated adipocytes, the up-regulation of SIRT1 results in inhibition of adipogenesis, enhanced lipolysis, and the release of FFAs [6]. Consistently with these results, the fasting Sirt1 heterozygous mice ($Sirt^{+/-}$) exhibit SIRT1 activation that, in turn, triggers a fat mobilization in WAT [6]. Moreover, the treatment of mice with a high-fat diet combined with either resveratrol or SRT1720 was found to reduce weight gain of these animals [26, 27].

Since adiponectin, an adipocyte-derived hormone with anti-inflammatory properties, affects energy homoeostasis as well as glucose and lipid metabolism, and since the adiponectin level is reduced in both obesity and type 2 diabetes [28], there is a growing interest in determining the underlying mechanisms that impair adiponectin gene expression in the above-mentioned metabolic disorders. Studies by Qiao and Shao have shown that SIRT1 up-regulates adiponectin gene expression by a FOXO1-C/enhancer-binding protein α (C/EBPα) complex, and moreover, both SIRT1 and FOXO1 protein levels are decreased in fat tissue from high-fat diet-induced obese and type 2 diabetic models, suggesting that changes in the expression level of these proteins may lead to impaired FOXO1-C/EBPα complex formation, and subsequently, to reduced adiponectin expression in obesity and type 2 diabetes [29].

It should be highlighted that spectacular experiments performed by Guarente *et al.* [30] with the use of SIRT1 transgenic mice revealed that these animals exhibited SIRT1 overexpression in WAT, brown adipose tissue (BAT), brain, and mouse embryonic fibroblasts (MEF), but not in liver and brain, and they displayed some phenotypes (e.g. increased metabolic activity, reduction of FFA, total cholesterol, and insulin levels in blood similar to mice on CR diet).

Pancreas

Pancreatic β cell are metabolic sensors which adjust insulin secretion to glucose levels in the bloodstream. The relationship between SIRT1 and insulin secretion by pancreatic β cell has been examined by two research teams (Bordone *et al.*, Moynihan *et al.*). Moynihan *et al.* [4] has revealed that β cell-specific SIRT1 overexpression enhances glucose-stimulated insulin secretion in transgenic mice and improves their glucose tolerance through the down-regulation of uncoupling protein 2 (UCP2), a mitochondrial inner membrane protein that mediates mitochondrial proton leak leading to reduction of ATP production [31]. On the other hand, Bordone *et al.* [5] has reported that knockdown of SIRT1 in β cell lines results in an increase of the UCP2 expression level and an impairment of insulin secretion. These findings suggest that SIRT1-mediated reduction of the UCP2 level in β cells could enhance ATP synthesis from glucose, which results in the closure of the ATP-dependent K^+ (K_{ATP}) channels, the stimulation of the voltage-gated Ca^{2+} channels, and the influx of extracellular Ca^{2+} (Fig. 3). The increased levels of intracellular Ca^{2+} lead to induction of insulin secretion [31]. It has been implied that changes in the NAD^+/NADH ratio in pancreas can regulate SIRT1 activity and insulin secretion in response to a diet since a significant decrease of the NAD^+ level in pancreas of the starved mice was observed [31]. These results support the role of either SIRT1 or UCP2 as physiologically relevant regulators of insulin production.

As mentioned previously, SIRT1 is a positive regulator of LXR [22]. Recently, it has been shown that LXR activation with T0901317 agonist in pancreatic β-cells leads to stimulation of both biosynthesis and secretion of insulin [32]. However, whether SIRT1 activates LXR in pancreatic β-cells remains yet to be elucidated.

Skeletal muscle

In humans, skeletal muscle is the major site of both glucose disposal, where approximately 80% of total body glucose uptake occurs under euglycemic hyperinsulinemic conditions [33], and the mitochondrial capacity for energy expenditure, where glucose or lipids is/are used for energy production. The direct link between nutrient deprivation and SIRT1 activation in muscle was reported by Gerhart-Hines *et al.* [34], who has revealed that low glucose levels stimulate SIRT1-mediated deacetylation of PGC-1α, leading to activation of genes involved in mitochondrial fatty acid oxidation, electron transport, and oxidative phosphorylation. Induction of these genes is essential in the case of a switch from glucose to fatty acid oxidation under low-nutrient conditions. Thus, SIRT1 can act as a sensor of nutrient adaptation through inducing fatty acid oxidation in response to low glucose concentrations. What is more, SIRT1 has recently been found to play a protective role in skeletal muscle by improving insulin sensitivity in this tissue through the transcriptional repression of tyrosine phosphatase 1B (PTP1B) gene [35]. PTP1B is a key insulin receptor phosphatase that directly dephosphorylates the insulin receptor, thereby it negatively regulates the insulin signal transduction cascade [35]. Interestingly, SIRT1 also deacetylates the insulin receptor substrate 2 (IRS2) favouring the IGF1 signalling in neuronal cells [36]. Thus, similar response may also occur in skeletal muscle but further work is needed in this regard.

Inflammation and SIRT1

Metabolic disorders, including obesity and insulin resistance/T2DM, are associated with a state of chronic low-grade inflammation. It has been shown that the levels of proinflammatory cytokines like TNF-α, IL-6, and C-reactive protein (CRP) are elevated in individuals with insulin resistance and diabetes [37]. Obesity causes microhypoxia in WAT and, in consequence, the release of proinflammatory cytokines (TNF-α and IL-6) and FFAs from adipocytes and macrophages, which subsequently can initiate proinflammatory responses by activating the JNK/activator protein 1 (AP1) and the IKK/NF-κB signalling pathways. The JNK and IKK/NF-κB pathways represent important modulators of inflammatory gene expression in many cell types, including skeletal muscles, liver, and WAT (Fig. 4) [37].

Several animal studies revealed the beneficial effect of SIRT1 action on metabolic disorders, suggesting that this effect may be mediated, at least in part, by the ability of SIRT1 to suppress inflammation in adipocytes, macrophages, and hepatocytes through inhibition of NF-κB transcriptional activity resulting from deacetylation of RelA/p65 subunit of NF-κB [38-41]. Thus, it becomes clear why the SIRT1 expression is inversely related to inflammatory gene expression in macrophages. Similarly, the SIRT1-overexpressing and resveratrol treated mice, in response to a high-fat diet, have the decreased NF-κB activity, which results in a reduced expression of proinflammatory cytokines, such as TNF-α and IL-6 [42, 43]. Consistently with this evidence, liver-specific SIRT1 null mice showed increased signs of

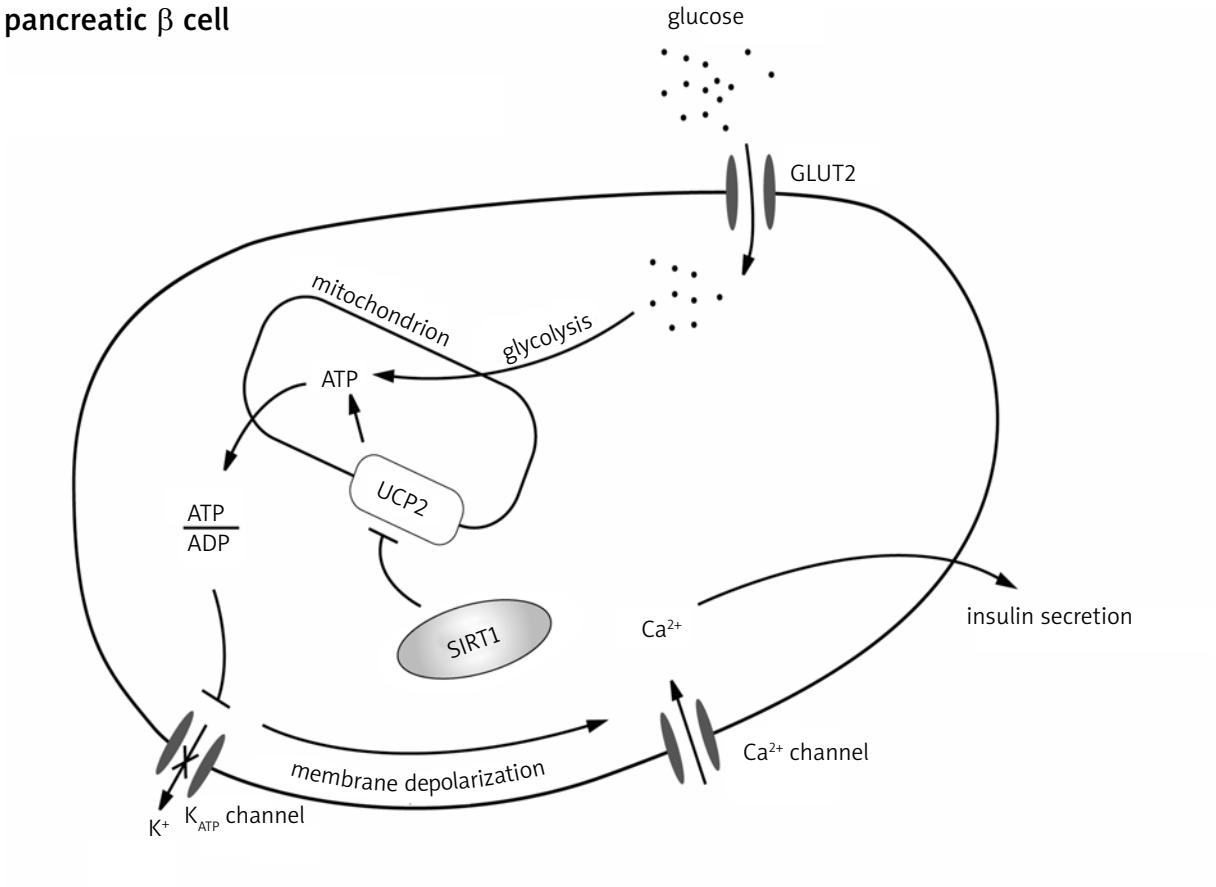

Fig. 3. SIRT1-mediated regulation of insulin secretion by β cells. A decrease of UCP2 expression by SIRT1 causes an increase of mitochondrial ATP production, leading to K_{ATP}-dependent depolarization of membrane and the influx of extracellular Ca^{2+} ions which enhance insulin secretion

inflammation and the NF-κB signalling when fed high-fat diet [44].

Independently of SIRT1-mediated deacetylation of RelA/p65 subunit of NF-κB, SIRT1 may affect NF-κB by regulating FOXO3a protein which suppress TNF-α-induced activation of NF-κB signalling [45, 46]. Additionally, several studies have demonstrated that the adiponectin levels are significantly diminished in both obesity and T2DM [28]. Interestingly, SIRT1 was found to be the major regulator of both transcription and secretion of adiponectin in adipocytes [47, 48]. Taken together, current studies support the hypothesis that SIRT1 inhibit inflammation, although the precise mechanisms by which SIRT1 may alter insulin sensitivity in several organs (e.g. liver, skeletal muscle, fat) remain to be elucidated.

Conclusions

Recent progress in understanding molecular defects in metabolic diseases, particularly in obesity and T2DM, has led to identification of sirtuins as novel therapeutic targets. Among these, focus on SIRT1 is of particular interest because it appears to interfere in a variety of important pathways generating or controlling these diseases and, moreover, this enzyme can be modulated pharmacologically by small molecules. In particular, resveratrol as SIRT1 activator has been found to improve insulin sensitivity, increase mitochondrial content, and prolong survival of mice fed a high-fat diet, thereby this polyphenol may be an attractive therapeutic agent for the treatment of T2DM. However, more animal and clinical data that support beneficial effects of resveratrol should be obtained and, additionally, other compounds such as SIRT1 activators or, perhaps in some cases even inhibitors, that might target specific tissues and function should be designed.

Abbreviations: FOXO1 – forkhead box 01A, LXR – liver X receptors, NAD – nicotinamide adenine dinucleotide, NAM – nicotinamide, NAMPT – nicotinamide phosphoribosyltransferase, NF-κB – nuclear factor κ-light-chain-enhancer of activated B cells, UCP2 – uncoupling protein 2, PGC1α – PPAR-γ coactivator-1α, PPAR-γ – peroxisome proliferator-activated receptor-γ, PTP1B – tyrosine phospha-

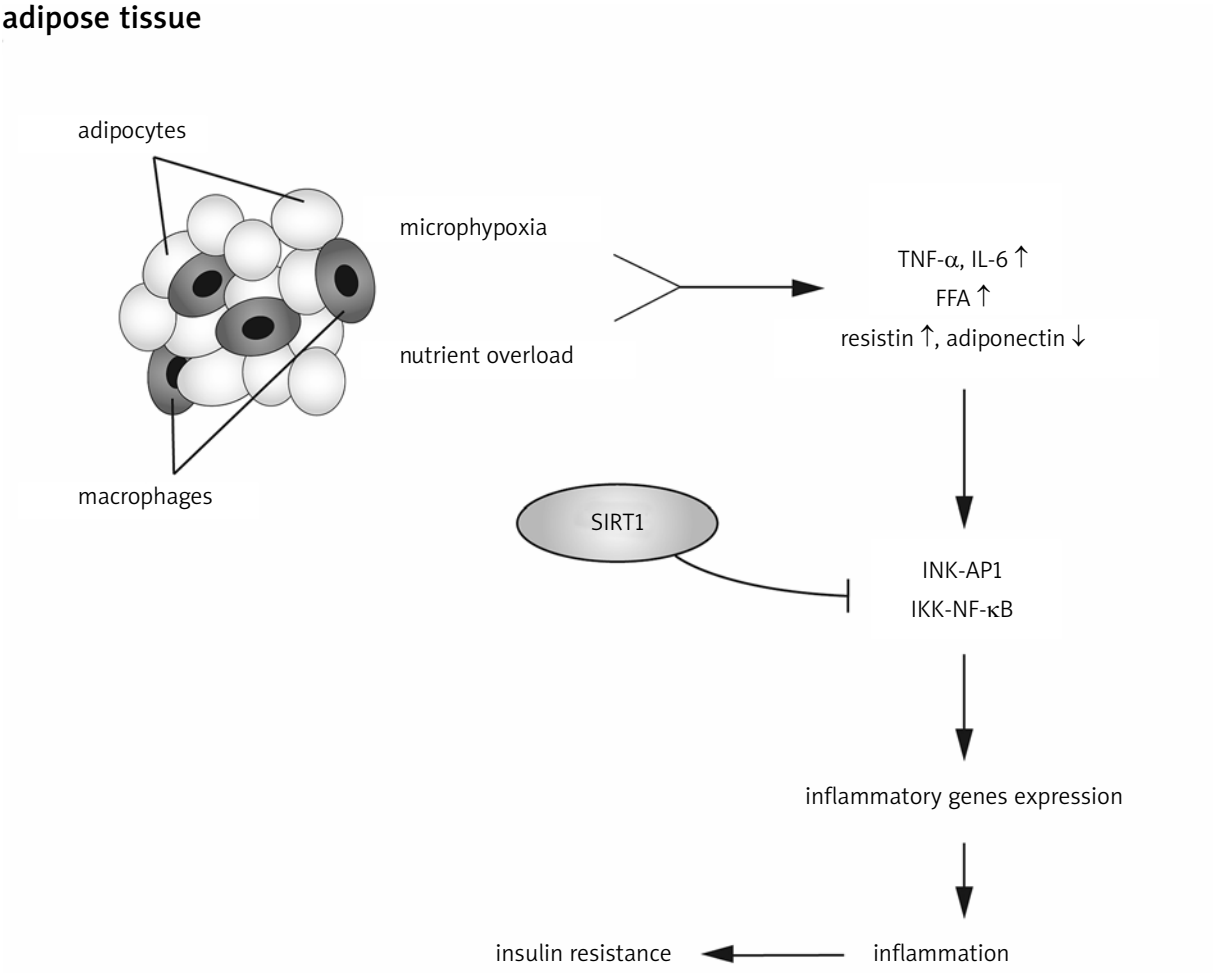

Fig. 4. SIRT1-mediated suppression of inflammation pathway. Microhypoxia in WAT stimulates a release of proinflammatory cytokines and FFAs which, in turn, induce the IKK/ NF-κB signalling pathway resulting in expression of inflammatory genes. SIRT1 inhibits inflammation through suppression of the NF-κB transcriptional activity. Activation → Inhibition ⊣

tase 1B, SIRT1 – silent mating type information regulation 2 homolog, STACs – sirtuin activating compounds, WAT – white adipose tissue.

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