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# Browning of Adipose Tissue and Sirtuin1 Involvement

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## Abstract

Obesity is an important risk factor for many diseases, including cardiovascular diseases, metabolic syndrome and cancers. Excessive dietary intake of caloric food results in its accumulation in white adipose tissue (WAT), whereas energy expenditure by fat utilization and oxidation predominately occurs in brown adipose tissue (BAT). Reducing obesity has become an important prevention strategy of research interest, focusing in the recent years, mainly on browning of WAT, the process during which the enhance of the mitochondria biogenesis occurs and then white adipocytes are converted to metabolically active beige adipocytes. Sirtuin1 (SIRT1), the most known isoform of sirtuin deacetylases, is implied in the browning of WAT process. In fact, it is a sensitive sensor of cell energy metabolism and, together with other sirtuin isoforms, contributes to this differentiation process. This chapter provides an overview about SIRT1 involvement in browning of WAT as a target molecule that can thereby contrast obesity.

**Keywords:** adipose tissue, browning, obesity, resveratrol, sirtuin1

## 1. Introduction

Lipids are stored in the body by two types of adipose tissue such as white adipose tissue (WAT) and brown adipose tissue (BAT) [1–3]; the main parenchymal cells of the adipose tissue are adipocytes, and so far two fat cell types, white and brown cells, have been reported, respectively [4–6]. The white and brown adipocytes arise from separate progenitor cell lines, present distinct structure, morphology, localization and functions [1, 5, 7] and these differences contribute to the maintenance and modulation of energy and of metabolic health [4, 8, 9].

Despite these differences, both types of adipocytes share the activity of accumulation and release of fatty acids and both express the rather specific adrenergic receptor β3 [10, 11].

The adipose tissue is highly dynamic in the sense that changes in mass of an order of magnitude can occur, this happen during physiological (like pregnancy/lactation or aging) and pathological states (like metabolic syndrome, obesity, etc.) [12, 13]. In physiological condition, functional WAT and BAT adipose tissues control and modulate the energy balance with important effects on metabolic health and longevity [6, 14]. Aging is typically associated with a body redistribution of adipose tissue (increased central, visceral and ectopic adiposity) [4, 6, 15, 16] and chronic low-grade inflammation [17, 18]. Aging is also related to an increase of lipotoxicity due to the reduced capacity of adipose depots to store free fatty acids [16, 19]. These conditions contribute to increased risk for metabolic perturbations such as insulin resistance, impaired glucose tolerance and diabetes [18, 20]. Of importance, key processes of adipose tissue physiology affect molecular pathways that regulate lifespan [21], such as sirtuins (SIRTs) levels decline with age in several tissues, including adipose tissue, and this reduction induces adipocyte dysfunctions leading to obesity [6, 22].

To date, in both advanced and developing countries, obesity has become a major health problem [7, 12, 23], mainly because it carries an increased risk of death for the associated disorders [24, 25]. In fact, excess WAT throughout the body is associated with an increased risk of cardiovascular diseases, breast, colon, oesophageal, gall bladder and pancreatic cancers, sleep apnea and physical disabilities, such as knee arthritis [26–28].

In the following sections, we present firstly the main differences between WAT and BAT and the WAT browning process and then we discuss the potential SIRT1 involvement in this process as a target molecule that can thereby contrast obesity, introducing also the effects of resveratrol as a SIRT1 exogenous inducer.

## 2. White adipose tissue

WAT is now known to be highly dynamic, synthesizing and secreting multiple lipids, proteins and autocrine, endocrine, paracrine and neuroendocrine factors which are involved in the regulation of a wide range of physiological and metabolic processes [4, 29]. In particular, white adipocytes, characterized by a large unilocular lipid droplet, have a low density of mitochondria and variable size (25–200 μm) [6, 7, 12, 29, 30] and they might secrete adipokines that are pro- and anti-inflammatory cytokines fundamental in the regulation of metabolic functions and also in the communication from adipose tissue to other tissues [7, 12, 31]. Other lipid molecules are also secreted by WAT, including prostanoids, cholesterol and retinol, which are stored in order to be subsequently released [4, 32].

The development of subcutaneous WAT begins in uterus, but primarily occurs after birth, when specialized fat storage cells are needed to provide fuel during fasting periods. Hyperplastic and hypertrophic white adipocyte processes occur during WAT development, throughout the organism's lifespan and in conditions of positive energy balance [33–35]. If the caloric excess is not reconciled by increased energy utilization, cellular hypertrophy and hyperplasia occur and then lead to adipocytes dysfunctions and so obesity [36, 37].

## 3. Brown adipose tissue

Since the 1970s, BAT has been increasingly recognized as the main site of nonshivering thermogenesis in mammals [35, 38] and it is probably the outcome of a single evolutionary development, in fact, unlike WAT, BAT is only found in mammals [35]. BAT adipocytes are smaller (15–60 μm) than white adipocytes [39] and present a characteristic brown color due to its high content of mitochondria and a lobulated surface that is innervated and very well vascularized [6, 8, 30]. BAT has the physiological role of metabolizing fatty acids in order to produce heat [4, 26], that is why it is often referred to as "good" fat, since it helps burn, not store, calories. This specific role of BAT is supported by the high content in its mitochondria of uncoupling protein1 (UCP1), uniquely expressed in these cells [4, 8, 26, 40]. The activation of UCP1 and transcriptional induction of the genes encoding UCP1 induce uptake of lipids and glucose from the circulation to sustain oxidation and thermogenesis [35, 41].

Functional BAT is more common in women than men and its mass and activity are reduced in overweight, obese and aging people [4, 41, 42]. Thus recruitment and activation of BAT seem to be a good tool to counteract obesity and its related diseases.

## 4. Browning of white adipose tissue

Currently, the terms browning, britening and beiging are used as synonyms to describe the differentiation of white adipocytes from brown adipocytes, so defined beige fat cells [30, 39, 43–45]. Browning of WAT is an adaptive and reversible response to numerous stimuli, including noradrenaline stimulation by cold exposure, exercise, natriuretic peptides, thyroid hormones, bile acids and nutritional compounds (resveratrol, menthol, capsaicin, etc.) [46, 47]. Other stimuli are due to pharmacological molecules, such as β3-adrenergic agonists, peroxisome proliferator-activated receptor γ (PPARγ) agonists thiazolidinediones and cannabinoid antagonist (rimonabant) [30, 48]. As a result of these stimuli, the transcriptional machinery of the browning program activates the expression of characteristic thermogenic genes (such as UCP1), leading to a beige adipocyte phenotype [30, 45, 47].

Two theories exist about the origin of beige adipocytes: (1) *de novo* differentiation from resident progenitor cells and (2) transdifferentiation. In detail, beige adipocytes can originate from progenitors resident within WAT that are differentiated in response to browning stimuli [39, 49–51] or, alternatively, they can arise via transdifferentiation, a process that involves the direct conversion of existing white adipocytes into brown-like fat cells [50]. This capacity of transdifferentiation is highly dependent on environment stimuli and also on the physiopathology aging [30, 52].

Beige adipocytes have a predominant lipid vacuole in the cytoplasm and numerous mitochondria, so exhibiting several intermediate features between white and brown adipocytes [33, 36, 47] (**Figure 1**), but these cells expressed characteristic and distinct gene markers that distinguished them from both white and brown fat cells [30, 39, 53, 54]. These genes encode proteins with very distinct cellular functions, including transcription factors (Zic1, Tbx15, etc.), metabolism-related proteins (Slc27a1, etc.) and proteins associated with inflammatory pathways
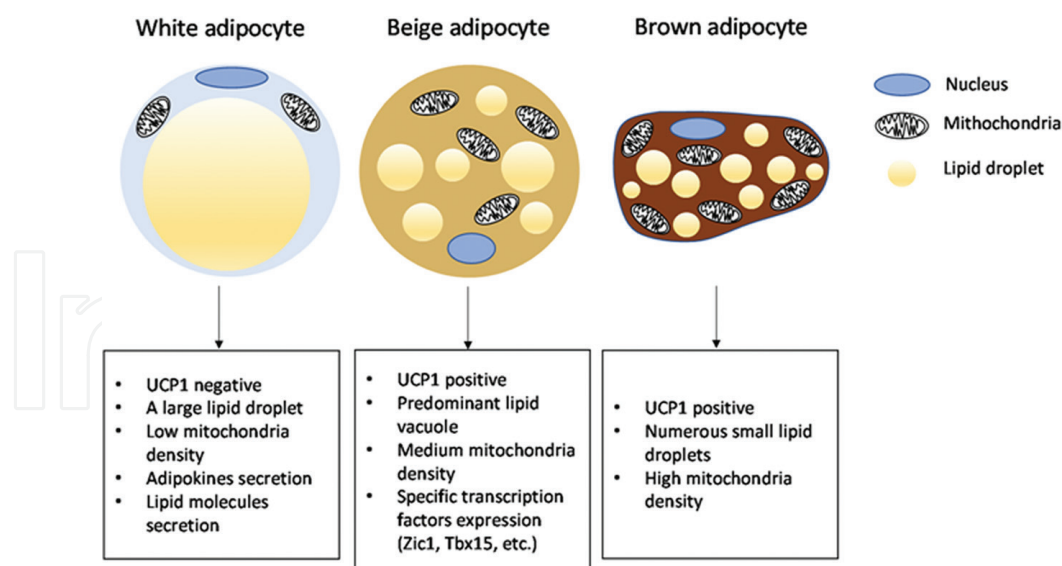
**Figure 1.** Main morphological characteristics of white, beige and brown adipocytes. UCP1: uncoupling protein 1.

(CD40, CD137, etc.) [35, 53–55]. It has been proved that more than 50 transcriptional molecules have been identified and their action mechanisms have been defined necessary in the browning transcriptional process [35, 56]. Among these, it is important to mention: PPARγ [50, 57], several members of the bone morphogenic protein family (BMP) [35, 58, 59], peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), which is involved in mitochondrial biogenesis [30, 33, 35] and also some transcription factors, such as C/EBPα and PRDM16 [58, 60, 61]. Even though the current terminology stresses the differences in cell lineage and localization, the evidence suggests that the beige adipocytes function as true thermogenic brown adipocytes [35, 47]. However, there is not a precise bioenergetic analysis of beige fat cells.

To date, the metabolic benefits of browning of WAT in humans remain to be fully established and the safety is a concern that must first be addressed regarding any method used to induce WAT browning. Cold exposure is a classic and efficient way to induce browning [62, 63], but its obvious discomfort, together with risks of hypothermia, makes it almost impractical for clinical use [50]. Therefore, browning agents, either endogenous or exogenous, provide an attractive alternative for limiting metabolic diseases.

Following paragraphs describe the potential SIRT1 involvement as a target molecule that can thereby contrast obesity, introducing briefly the effects of resveratrol as a SIRT1 inducer.

## 5. Sirtuins

SIRTs are NAD$^+$-dependent deacetylases present in all prokaryotic and eukaryotic cells (with the exception of several red *algae* and *archaea*) [64, 65]. Mammals possess seven isoforms, from 1 to 7, mainly known as anti-aging molecules [66–69]; however they are involved also in the regulation of numerous other cellular processes, such as integrity of chromatin [70, 71], cell cycle [72, 73], apoptosis [74, 75], energy metabolism [76–78], inflammation [79, 80] or detoxification [81, 82]. Their expression occurs throughout whole body differing in their cellular

localization (mitochondrion, cytoplasm or nucleus) and tissue distribution [81, 83–88] (**Table 1**). Biochemically, SIRTs are a class of proteins that posses mainly NAD$^+$-dependent lysine deacetylase activities [89, 90]; however, some particular isoforms, like SIRT4 or SIRT6, also hold ADP-ribosyl transfer activity [91, 92]. SIRT isoforms share a conserved core catalytic domain, a NAD$^+$-binding place, consists of two subdomains [93]. SIRT isoforms' structural differences are manifested at N- and C-terminal regions, which are variable among homologs and enable them to possess more than one type of catalytic activity [94].

So far, more than 30 SIRTs substrates were identified and, in general, are divided into two groups: histones and non-histone substrates and deacetylation of both is a quick response to stress stimuli or activators [95, 96]. SIRTs also serve as the regulators of transcription of genes in complex with other transcription factors [97].

Among the SIRT isoforms, the most attention has been focused on SIRT1, the ortholog of yeast Sir2 [64, 98]. During aging, its levels decrease [99] and this reduction occurs also during age-associated diseases (like neurodegenerative pathologies, cardiovascular diseases, metabolic syndrome, etc.) [100–102] making SIRT1 a possible treatment target. In fact, the beneficial effects of SIRT1 activation have been shown on numerous animal models [103–106] as well as humans [107–109]. Additionally, the positive effects of SIRT1 activation include also browning of WAT [110–112].

### 5.1. Sirtuin1 involvement in browning of white adipose tissue

All seven SIRT isoforms are expressed in adipose tissue [113–118], where they hydrolyse acetyl- and/or other acyl-group from the lysine residue of target substrate [119–121]. After particular stimuli, as summarized in **Figure 2**, the activation of SIRT1 at WAT level occurs and leads to the modulation (deacetylation) of PPARγ [110, 122], that with PRDM16 and PGC-1α, promote transcription of genes specific of BAT [61, 123].

Furthermore, PPARγ induces binding of C/EBPα and carboxy-terminal binding proteins 1 and 2 (CtBP 1 and 2) and represses transcription of genes which are specific of WAT [61, 124]. Thus, through PPARγ, SIRT1 is involved not only in enhancement of transcription of BAT genes, but also in repression of WAT genes. Furthermore, SIRT1 promotes mito-

| Enzyme | Localization | Activity |
|--------|-------------|----------|
| SIRT1 | Nucleus, cytoplasm | Deacetylase |
| SIRT2 | Nucleus, cytoplasm | Deacetylase |
| SIRT3 | Mitochondria, nucleus, Cytoplasm | Deacetylase |
| SIRT4 | Mitochondria, cytoplasm | ADP-ribosyltransferase, lipoamidase, deacetylase |
| SIRT5 | Mitochondria, cytoplasm, nucleus | Malonyl-, sukcinyl-, glutaryl-deacylase |
| SIRT6 | Nucleus, endoplasmatic reticulum, cytoplasm | Deacetylase, ADP-ribozyltransferase, long-chain fatty acids deacylase |
| SIRT7 | Nucleus (nucleolus), cytoplasm | Deacetylase |

**Table 1.** Localization and catalytic activity of mammalian sirtuin isoforms.
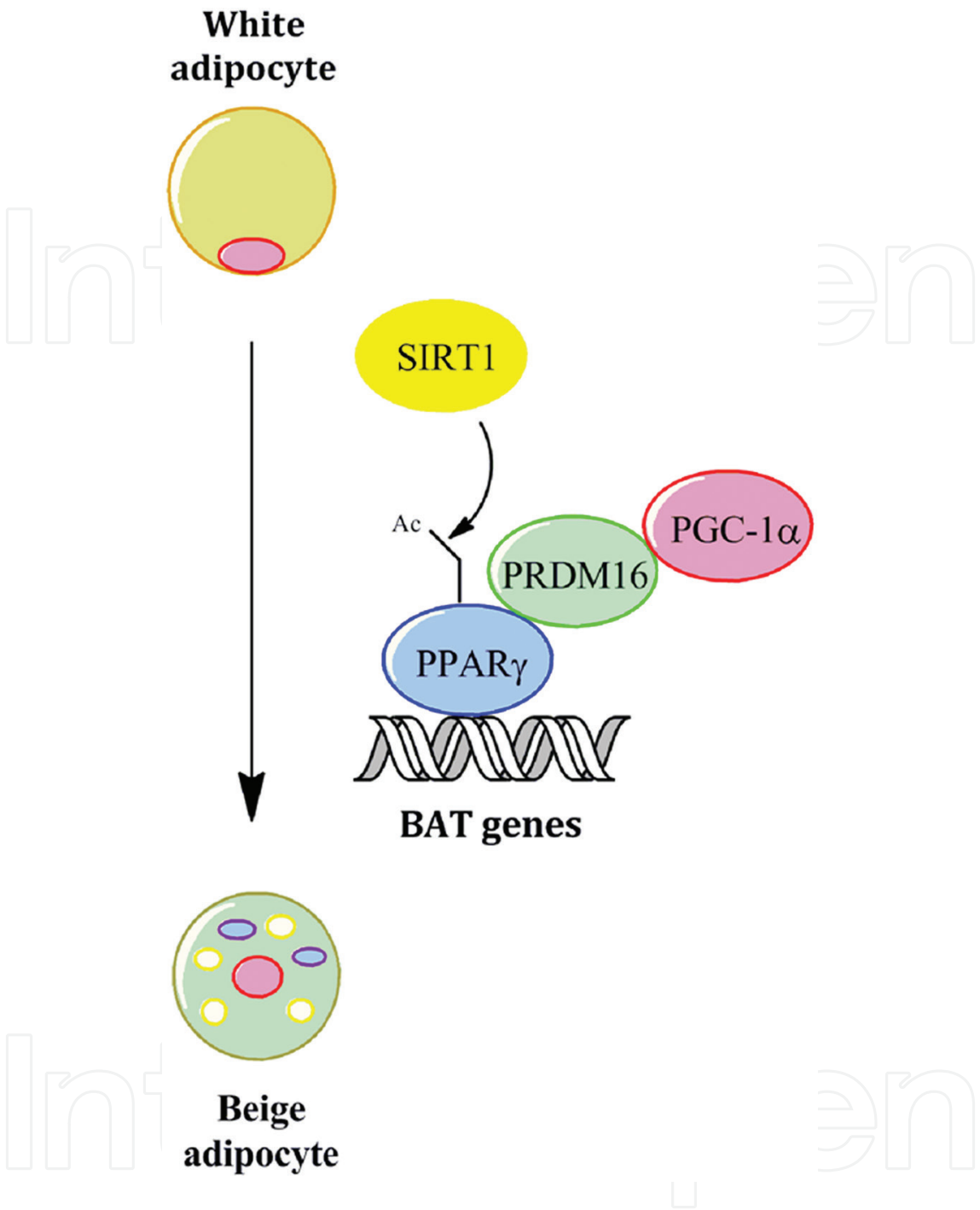
**Figure 2.** Involvement of sirtuin1 in browning process of white adipocyte. Sirtuin1 deacetylates PPARγ which than create a transcription complex with PRDM16 and PGC-1α promoting the beige adipocyte formation. SIRT1: sirtuin1; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PPARγ: peroxisome proliferator-activated receptor γ.

chondrial biogenesis by activating PGC-1α [125]. PGC-1α regulates also transcription of mitochondrial SIRT3, which is necessary for the full acquirement of BAT phenotype [117, 126]. In detail, PGC-1α promotes the transcription of SIRT3, which mediates the phosphorylation of CREB with subsequent enhanced expression of UCP1 and PGC-1α [117, 127]

(**Figure 3**). Furthermore, SIRT3 is involved in the regulation of many steps of mitochondrial metabolism, such as deacetylation of subunits of electron transport chain, for maintaining mitochondria proper functions [127–129].

Moreover, SIRT1 in adipose tissue might also decrease fat storage, promote lipolysis and protect against obesity-induced inflammation [130, 131]. Fang et al. [132] described a mechanism of regulation of SIRT1 activity by SIRT7, in detail, SIRT1 is able to augment its own catalytical activity by autodeacetylation and SIRT7 binds to SIRT1 and inhibits its activity. These data will help to clarify the mechanism of obesity in humans who showed decreased SIRT1 and increased SIRT7 in visceral adipose tissue in comparison to healthy normal-weight subjects [114]. However, Rappou
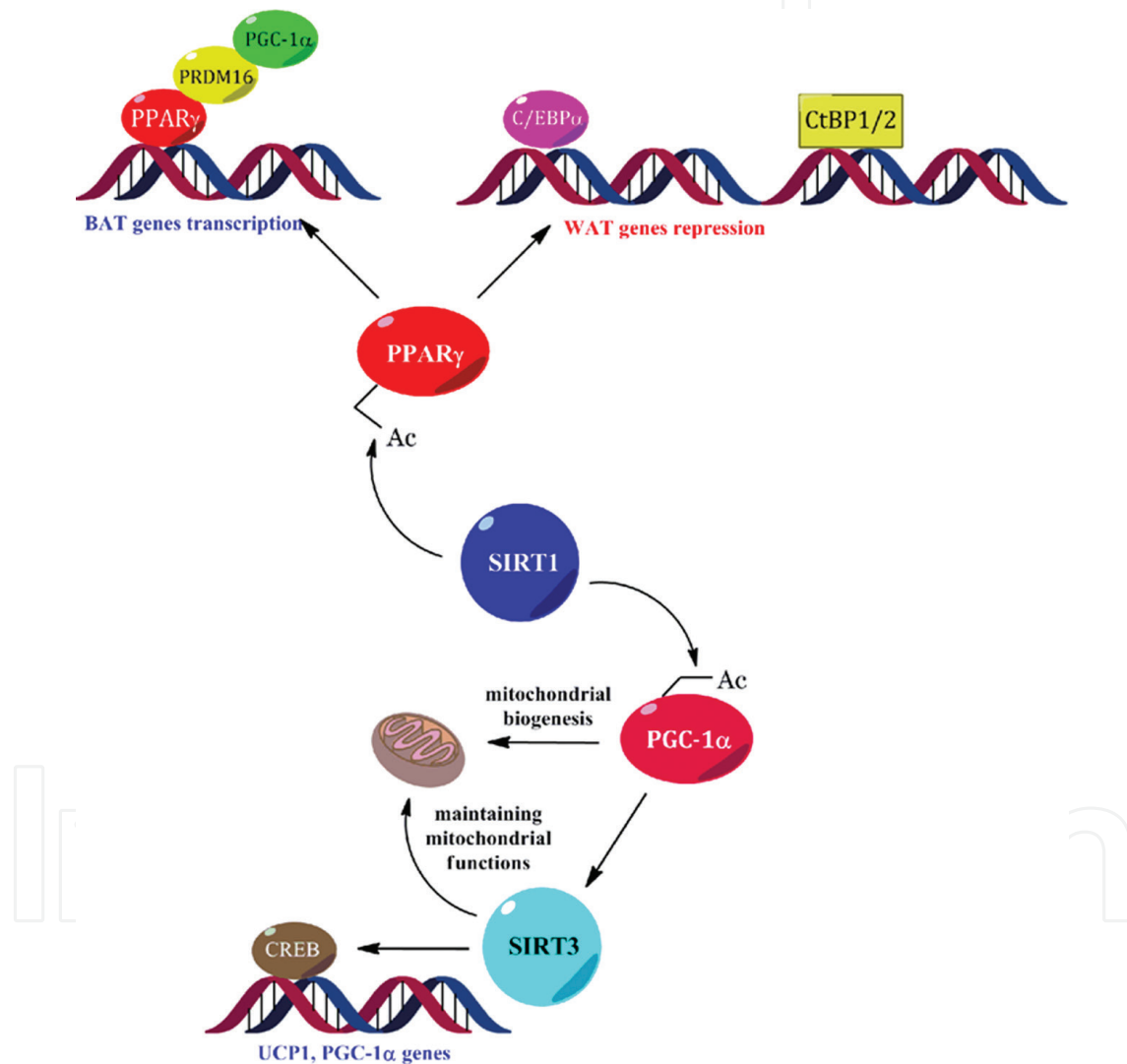


**Figure 3.** Sirtuin1 and sirtuin3 involvement in browning process. Sirtuin1 deacetylates PPARγ, which subsequently activates brown adipose tissue gene transcription and represses white adipose tissue genes. Sirtuin1 deacetylates also PGC-1α, which enhances mitochondrial biogenesis and sirtuin3 transcription, that is involved in maintaining mitochondrial functions and transcription of brown adipose tissue genes. CtBP 1/2: carboxy-terminal binding proteins 1 and 2; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PPARγ: peroxisome proliferatoractivated receptor γ; SIRT1: sirtuin1; SIRT3: sirtuin3; UCP1: uncoupling protein1; WAT: white adipose tissue.

et al. [133] investigated the subcutaneous adipose tissue changes of all SIRT isoforms in obese subject with respect to normal-weight individuals and found decrease not only in SIRT1 and SIRT7 expression, but also in SIRT3. Moreover, they observed in the obese group that the continuous weight losers showed higher levels of SIRT1 in comparison to weight maintainers, suggesting that the individuals with naturally higher level of SIRT1 could be helped in weight loss.

Taken together, these data suggest that SIRTs, mainly SIRT1, could be strategic target in prevention and treatment of obesity and relative diseases. In fact, SIRTs activation results in many health benefits, including repression of adipogenesis [134] and promotion of browning of WAT [135, 136].

Polyphenolic compounds, among which the most studied in relation with SIRTs is resveratrol, might be dietary activators of SIRT1 [137–139]. Resveratrol is present in foods, like black and red grapes, blueberries, dark chocolate and peanuts [140–142]. In humans, its consumption protects low-density lipoprotein particles against oxidation promoting vascular health, decreases inflammation reducing C-reactive protein, tumor necrosis factor-$\alpha$ and interleukin-6 and also inhibits reactive oxygen species production [143–145]. Remarkably, resveratrol supplementation induced browning of WAT not only in rodents [146, 147], but also in human [135]. SIRT1 activation by resveratrol decreased PPAR$\gamma$ acetylation in 3T3-L1 white adipocytes and in human subcutaneous adipose tissue [110]. Furthermore, the overexpression of SIRT1 did not affect adipogenesis, but selectively decreased representative WAT genes [110]. This is in accordance with observations of Andrade et al. [146] who used resveratrol as SIRT1 activator in diet and showed attenuated expression of PPAR$\gamma$ and increased in UCP1 expression, contributing to loss of fat mass in comparison with mice fed without resveratrol.

It is interesting to cite also capsaicin as an inducer of WAT browning process through SIRT1 activation. The capsaicin, an irritant component of chili peppers [148], is not a direct activator of SIRT1, but it activates AMPK which, in turn, activates SIRT1 [149]. It may relieve neuropathic pain [150], osteoarthritis [151], migraine, headaches [152] or psoriasis [153] and it was studied also as a potent inducer of browning process [149, 154, 155]. Baskaran et al. [119] showed that the addition of 0.01% of capsaicin to high fat diet suppressed weight-gain in mice together with decrease in lipid content of epididymal and subcutaneous adipocytes. Furthermore, significant increase of SIRT1 and then of UCP1, PPAR$\gamma$, PGC-1$\alpha$ and PRDM16 expression, promotes browning of WAT. However, it is difficult to study the effects of capsaicin in human due to low tolerance to capsaicin.

Resveratrol and capsaicin, together with other natural compounds, for example, green tea extracts, curcumin, melatonin or $\omega$-3 polyunsaturated fatty acids [156, 157] and non-dietary inducers, such as endurance training and cold exposure [158], may represent interesting and promising stimuli of WAT browning process.

## 6. Conclusion

In summary, SIRT1 will be considered as an essential regulatory protein in browning of WAT. As BAT amount and SIRT1 expression decreased with age, targeted activation of SIRT1 is a promising strategy to stimulate browning of WAT. Activation of SIRT1 could be a novel

strategy in obesity treatment and related disorders. However, further studies are needed to better clarify the involvement of SIRT1 in the browning of WAT process and to identify more efficient SIRT1 inducers, which possess minimum side effects.

## Conflict of interest

The Authors declare no conflict of interest.

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