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Review

The Role of Sirtuin-1 (SIRT1) in the Physiology and Pathophysiology of the Human Placenta

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Abstract: Sirtuins, especially SIRT1, play a significant role in the regulation of inflammatory response, autophagy, and cell response to oxidative stress. Since their discovery, sirtuins have been regarded as anti-aging and longevity-promoting enzymes. Sirtuin-regulated processes seem to take part in most prevalent placental pathologies, such as preeclampsia. Furthermore, more and more research studies indicate that SIRT1 may prevent pre-eclampsia development, or at least alleviate its manifestations. Having taken this into consideration, we have made a review of recent studies on the role of sirtuins, especially SIRT1, in the regulation of processes determining normal or abnormal development and functioning of the placenta.

Keywords: sirtuin-1; SIRT1; sirtuins; human placenta; placental physiology; placental pathophysiology; preeclampsia; peroxisome proliferator-activated receptor γ ; PPAR γ ; SIRT1/PPAR γ signaling

1. Introduction

Placenta is a unique organ occurring during intrauterine life, playing a significant role in the regulation of fetal growth and development [1, 2]. It consists of trophoblast-derived epithelial cells, outer layer of blastocyst, and extraembryonic mesodermal cells that derive from inner cellular mass – a group of cells which give rise to embryo proper [3]. In the course of placentation, this combination of cells gives rise to a complex organ which anchors the fetus in the uterine cavity and provides delivery of oxygen, nutrients and hormones required for fetal growth, as well as the excretion of carbon dioxide and other end products of metabolism. While extraembryonic mesodermal cells give rise to mesenchymal parts of the placenta, including fetal circulatory system, trophoblast-derived epithelial cells differentiate to form two main layers of the trophoblast: villous trophoblast (called labyrinthine layer in mice) and extravillous trophoblast (called junctional zone in mice). While villous trophoblast takes part in gas and nutrient exchange, extravillous trophoblast anchors the placenta in the uterine wall and remodels maternal spiral arteries to provide sufficient perfusion of fetoplacental unit [4]. Impaired placental development or function may have significant consequences both for the mother and for the fetus, resulting in complications such as pregnancy-induced hypertension/preeclampsia, intrauterine growth retardation, gestational diabetes, macrosomia, or even accelerate the termination of a pathological pregnancy through miscarriage, stillbirth, and preterm birth [5]. Furthermore, some research studies suggest that gestational complications, especially those resulting in the intrauterine growth retardation, can have a long-term effects even in postnatal life, contributing to metabolic programming which can increase the risk of obesity, diabetes, and cardiovascular disease later in life [6]. This is why there is a need of deeper understanding of placental development, especially in reference to some signaling pathways that can affect fetal growth.

Sirtuins, which are a highly conserved group of epigenetic proteins, play an important role in the comprehensive regulation of metabolic processes at the cellular level. A detailed understanding of their physiological and altered expression in the human placenta may provide a lot of valuable information about the physiology of the placenta and the mechanisms of development of placental

pathologies. Much of the latest placental research, the results of which we cite and discuss in this review, concerns sirtuin-1 (silent information regulator 2 homolog 1 or SIRT1), a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase [1,7,8].

2. SIRT1 in the regulation of trophoblast function

2.1. Effects towards placental development and differentiation

SIRT1 is very important for proper trophoblast differentiation and placental development [1, 5, 7, 9,10]. In placentas and serum samples collected from patients with preeclampsia (PE), SIRT1 activity is reduced and can be observed mainly in cell nuclei within cytotrophoblast and syncytiotrophoblast [11,12]. SIRT1 probably takes part in trophoblast maintenance and differentiation through modulating small mothers against decapentaplegic proteins 2/3 (SMAD2/3), signal transducer and activator of transcription (STAT), and peroxisome proliferator-activated receptor γ (PPAR γ)-dependent signaling pathways [13–16]. Placentas collected from SIRT1 KO pregnant mice are small and show visible abnormalities both within labyrinthine layer and junctional zone [11]. In addition, trophoblast stem cells (TSC) collected from SIRT1 knockout (KO) mice show impaired differentiation.. In such cells, PPAR γ expression is reduced, along with the expression of such proteins as SMAD2, SMAD3, and signal transducer and activator of transcription 3 (STAT3). STAT3 protein is correlated with differentiation of trophoblast giant cells, while its molecules can be deacetylated by SIRT1, which represses their activity [14, 17, 18]. Moreover, a possible role of PPAR γ in placentation and trophoblast differentiation is emphasized [13,19], and PPAR γ activity may be regulated by SIRT1, both through deacetylation and through recruitment of cofactors such as nuclear receptor co-repressor-1 (NCoR1), silencing mediator of retinoid and thyroid hormone receptors (SMRT), and positive regulatory domain containing 16 (Prdm16) [20, 21]. Results of research studies made so far suggest that labyrinthine layer of trophoblast is poorly developed in SIRT1 \pm mice, while trophoblast invasive capability is also reduced, being even more reduced in SIRT1 KO mice [22], which may indicate that SIRT1 plays an important role in placental development and differentiation.

2.2. Effects of SIRT1 on autophagy within trophoblast

Autophagy is a cell homeostasis-promoting process directing damaged proteins and organelles to lysosomal degradation [23–27]. Autophagy protects the placenta from pathogens and stress. In PE patients, autophagy in trophoblast is impaired, and accumulation of abnormal proteins within the placenta is increased [28]. Several research studies have shown that SIRT1 prevents H₂O₂-induced oxidative stress and apoptosis through promoting autophagy within trophoblast [29]. From the mechanistic standpoint, some studies on autophagy-mediating proteins have shown that SIRT1 may regulate autophagy through NAD⁺-dependent deacetylation of some of them, e.g. transcription factor EB (TFEB), LC3-II – a membrane-bound (lipidated) form of microtubule-associated protein 1 light chain 3 (LC3), protein that contains a Bcl-2 homology-3 domain (Beclin-1), ubiquitin-binding scaffold protein (p62, also known as sequestosome 1, SQSTM1), autophagy related-proteins 5, 7 and 8 (ATG5, ATG7 and ATG8, respectively) [30, 31]. Formation of lysosomes taking part in autophagy is strictly regulated by TFEB which can be deacetylated by SIRT1, subsequently activating the expression of several downstream autophagy-related genes, such as lysosomal associated membrane proteins 1 and 2 (LAMP1, LAMP2), and cathepsin D (CTSD) [32,33]. Furthermore, concentrations of protein markers typical for the initial stage of autophagy activation, such as LC-II, Beclin-1 and SQSTM1 [34–36] have been also significantly altered in the course of PE and can be regulated by SIRT1 [37–39]. These results taken together suggest that SIRT1 may regulate autophagy within the trophoblast through deacetylation of its specific target proteins taking part in the process of autophagy.

2.3. Effects on cell senescence phenotype occurrence within the placenta

Premature senescence of the placenta is a trait typical for PE. It manifests with increased occurrence of cell senescence phenotype (CSP), senescence-associated secretory phenotype (SASP) and enhanced expression of such cell senescence markers as protein encoded by the TP53 tumor

suppressor gene (p53) and cyclin-dependent kinase inhibitor p21 (p21). Loss of SIRT1 activity is also a specific marker of cell senescence, and SIRT1 deficiency results in a premature senescence within placentas during their formation [40–43]. Interestingly, Xiong et al. have found that reduced SIRT1 activity promotes p53 acetylation and p21 expression, as well as impairs trophoblast cell migration and invasion in case of advanced maternal age, which suggests that SIRT1 deficiency can take part in the pathogenesis of PE through inducing CSP within the placenta.

2.4. Effects of other sirtuins towards trophoblast

There are seven sirtuins in mammals (SIRT1 – SIRT7). All of them deacetylate specific target proteins, using NAD⁺ as a co-substrate, as well as take part in the regulation of such processes as oxidative stress response, energy metabolism, inflammatory response etc. [44]. Several research studies have revealed that sirtuins play a significant role in trophoblast development and differentiation. This does not only apply to SIRT1. For example, SIRT2 is normally expressed in placental syncytiotrophoblast, and its expression is reduced in PE patients. SIRT2 may induce trophoblast cell necrosis while inhibiting trophoblast cell proliferation [45,46]. SIRT3 is reported to affect trophoblast cell migration, invasion, and tube formation, as well as to take part in the pathogenesis of PE [47]. SIRT4 can also induce trophoblast cell senescence [48–50]. These results may additionally confirm the hypothesis that SIRT1 deficiency can take part in the pathogenesis of PE through regulating trophoblast cell invasion, migration and proliferation.

3. SIRT1 and PPAR γ

Peroxisome proliferator-activated receptor γ (PPAR γ) belongs to the family of nuclear hormonal ligand-activated receptors. It can also act as transcription factor, widely known because of its crucial role in glucose and lipid metabolism, as well as in adipocyte differentiation. After dimerization with retinoid X-receptor (RXR), PPAR γ binds specific DNA sequences defined as PPAR γ -reactive elements (PPRE) and subsequently induces genes involved in fatty acid assimilation and accumulation, which results in lipid accumulation and adipogenesis. PPAR γ is actually necessary for formation of both white and brown adipose tissue, with white adipose tissue being the site of energy storage and hormone secretion, while brown adipose tissue being the site of energy expenditure and thermogenesis. PPAR γ may be activated by thiazolidinediones (TZD) – synthetic activators that are sometimes used in the treatment of type 2 diabetes mellitus [51,52].

Sirtuin 1 (SIRT1) is a member of NAD⁺-dependent protein deacetylases, at the same time functioning as a sensor of cell nutritional status. Its orthologue has been initially discovered in budding yeast, *Saccharomyces cerevisiae* as a longevity-promoting enzyme. SIRT1 has been first identified as a histone deacetylase, promoting chromatin compaction and silencing transcription of some genes in case of undernutrition [53]. However, more recent studies have identified numerous non-histone substrates of SIRT1, including p53, forkhead O class box transcription factors (FoxOs), and PPAR γ . Through deacetylating PPAR γ , SIRT1 renders its inactivation, thus inhibiting adipogenesis and promoting fat mobilization at the same time. On the other hand, inhibition of SIRT1 expression with small interfering RNA (siRNA) promotes adipogenesis and inhibits lipolysis [54]. In addition to its effects on metabolism, SIRT1 regulates many other signaling pathways, including those involved in cell proliferation, apoptosis, autophagy, and inflammatory response [55,56]. SIRT1 can be activated both by a naturally occurring compound – resveratrol which has been identified as anti-inflammatory and anti-oxidative agent, and by small molecule synthetic activators [57].

Although SIRT1 inhibitory action towards PPAR γ has been studied quite well, the interaction between these two proteins is not so simple. It has been found that PPAR γ deacetylation by SIRT1 results in the recruitment of positive regulatory (PR) domain zinc finger protein 1 (PRDM1) coactivator, which selectively activates PPAR γ to stimulate conversion of white adipose tissue to brown adipose tissue [58]. Furthermore, PPAR γ can be also an upstream inhibitor of SIRT1, both through inhibiting its deacetylase activity and through inhibiting its expression at the level of transcription [59]. Finally, both thiazolidinedione PPAR γ activators and SIRT1 activators, such as resveratrol, may exert collateral effects. TZD induce a transient overexpression of SIRT1 [60], while

resveratrol binds some nuclear receptors from PPAR family, including PPAR γ [61]. Thus, evaluation of cross-talk between signaling pathways dependent on these two proteins requires a thorough analysis of experiment results, especially if activators of both proteins are used.

3.1. Role of SIRT1- and PPAR γ -dependent signaling pathways in placental pathology

Impaired trophoblast differentiation and placental development are correlated with many complications of pregnancy, including miscarriage, pre-eclampsia, intrauterine growth retardation, and gestational diabetes [62–64]. These complications are related to a suboptimal microenvironment at the maternal side of the placenta, showing signs of hypoxia, oxidative stress, inflammation, and/or hyperglycemia. This is why it should be stated how those alterations in the placental microenvironment may affect SIRT1 and PPAR γ -dependent signaling in the placenta.

3.1.1. Effects of hypoxia on PPAR γ activity

Oxygen tension is an important parameter within the placenta, both in the course of normal development and specific placental pathologies [65]. During hypoxia, i.e. when oxygen tension is too low, many signaling pathways are activated, subsequently affecting tissue homeostasis. Relatively best known among them is a signaling pathway activated by hypoxia-inducible factor (HIF) which is a complex of two component proteins: hypoxia-inducible factor subunit alpha (HIF α) domain that is stabilized with oxygen, and hypoxia-inducible factor subunit beta (HIF β) domain that is expressed constitutively [66]. HIF-dependent signaling pathway is necessary for both placental formation and development, especially for trophoblast differentiation to invasive cell line (trophoblast giant cells in mice, corresponding to human extravillous trophoblast) [67–69]. It is known that hypoxia affects PPAR γ activity through HIF complex, and thus hypoxia inhibits adipocyte differentiation through its effect on HIF-dependent PPAR γ 2 – an isoform of PPAR γ typical for adipose tissue [70]. In mouse trophoblast stem cells, hypoxia inhibits PPAR γ activity, but this effect is independent from HIF activity. [71]. In addition, forced PPAR γ expression in the course of hypoxia may in part rescue trophoblast cell differentiation into labyrinthine layer in mice [71].

The results presented above correlate with hypoxia-associated placental pathology, occurring in the course of pre-eclampsia at the maternal site. Abnormal differentiation of syncytiotrophoblast which is an analogue of labyrinthine layer of trophoblast in mice, is a typical feature of this condition, regarded as secondary to reduced blood supply to the maternal part of the placenta because of abnormal remodeling of spiral arteries by invasive cells of extravillous trophoblast [5]. Placentas collected from PE patients show a reduced expression of PPAR γ , as well as decreased activity of glial cells missing-1 (GCM1) – a main regulator of syncytiotrophoblast formation and probably a target protein for PPAR γ . GCM1 can in turn activate protein referred to as syncytin-1 [72–74] and trophoblast abnormalities similar to those occurring in the course of PE have been recapitulated in vitro through repressing the level of GCM1 [75]. Therefore, it is presumed that reduced PPAR γ activity as a result of hypoxia may inhibit GCM1 and syncytin-1 expression, which in turn negatively affects syncytiotrophoblast differentiation.

Another finding typical for PE is elevated level of anti-angiogenic molecule - soluble vascular endothelial growth factor (VEGF) receptor, also known as soluble fms-like tyrosine kinase 1 (sFlt-1), in maternal blood [76]. Although etiology and origin of increased sFlt-1 release from placentas in PE patients is still a debate subject, several studies have shown a correlation between hypoxia and increased sFlt-1 expression in human trophoblast [77–80]. Some studies reveal a correlation between sFlt-1 level in syncytiotrophoblast and severity of PE manifestations [81,82]. PPAR γ activity has been negatively correlated with increased sFlt-1 level in the rat model of PE, pregnant female rats show PE symptoms, such as arterial hypertension, proteinuria and fetal growth retardation when treated with PPAR γ antagonist. These symptoms are associated with an increased sFlt-1 concentration in the plasma [83]. Quite interestingly, one separate study on mice has shown a correlation between reduced level of GCM1 and raised level of sFlt-1 in the plasma [84]. Combined results of these studies suggest that PPAR γ -GCM1 axis can take part in regulating sFlt-1 expression. When evaluating the levels of sFlt-1 mRNA and sFlt-1 release from differentiated mouse trophoblast stem cells (TSC) after

their treatment with PPAR γ activator, rosiglitazone, reduced levels of both sFlt-1 mRNA and sFlt-1 release can be found. Rosiglitazone does not affect sFlt-1 level in wild-type TSC (WT TSC) exposed to hypoxia and in PPAR γ KO TSC exposed to normoxia or hypoxia, which suggests that the observed effect is PPAR γ -dependent.

Finally, PE is characterized by increased occurrence of apoptosis in trophoblast cells [85], which is interesting, because PPAR γ is one of molecules involved in apoptosis. When trophoblast cells are cultured under hypoxic conditions, their differentiation to form syncytiotrophoblast is impaired, and severe hypoxia leads to apoptosis [86,87]. In similar conditions, treatment of these cells with PPAR γ activator – rosiglitazone – promotes their normal differentiation and alleviates apoptotic damage [86]. These results combined may be a premise to regarding PPAR γ as a potential target protein in the treatment of placental pathologies, such as PE.

3.1.2. Effects of hypoxia on SIRT1 activity

In comparison to correlations between hypoxia and PPAR γ activity, correlation between hypoxia and SIRT1 activity seems to be more complex. In several research studies, SIRT1 has been identified as an upstream regulator of HIF α domains. SIRT1 may deacetylate hypoxia-inducible factor 1 subunit alpha (HIF-1 α), which results in blocked recruitment of p300 domains and thus abrogate the expression of HIF-1 α effector genes [88]. In addition, SIRT1 selectively stimulates the activity of hypoxia-inducible factor 2 subunit alpha (HIF-2 α), thus promoting hypoxia-related signaling dependent on this alternative HIF α domain [89]. Moreover, SIRT1 gene expression can be impaired by hypoxia in a HIF-dependent manner, which suggests a feedback loop between these two proteins [90]. SIRT1 expression within trophoblast under hypoxic conditions has not been evaluated in details. However, one study has shown SIRT1 induction during hypoxia in human trophoblast cells, which results in upregulation of N-myc downstream regulated gene 1 (NDRG1) and reduced expression of p53, thus promoting cell survival [91]. Nevertheless, more detailed studies are thought to be necessary for pinpointing precise and detailed correlations between hypoxia, HIF activity, and SIRT1 activity, both in trophoblast and in placenta.

Similarly to PPAR γ , SIRT1 activity has been found to be reduced within syncytiotrophoblast isolated from PE patients placentas [92]. It is hypothesized that this result is related to increased CSP occurrence among trophoblast cells in the course of PE, especially when having taken SIRT1 longevity-promoting function into consideration [92]. In several studies, SIRT1 activity has also been negatively correlated with the severity of PE manifestations. In one of them, SIRT1 activator – resveratrol – has been shown to inhibit sFlt-1 release induced by the treatment of human placentas with tumor necrosis factor alpha (TNF- α) or by exposing them to hypoxia. Resveratrol also reduces sFlt-1 release from placental explants collected from PE patients, although only by 25-30% [93]. In a more recent study, exposal of primary human trophoblast cells to resveratrol has been found to inhibit both sFlt-1 secretion and sFlt-1 mRNA transcription [94]. Also in differentiated mouse WT TSC and SIRT KO TSC, treatment with resveratrol inhibits both sFlt-1 secretion and sFlt-1 mRNA transcription in a SIRT1-dependent manner. Since PPAR γ activity also falls with SIRT1 KO [11], there is probably more than one target protein through which SIRT1 regulates basic levels of sFlt-1. Finally, resveratrol has also been reported to alleviate arterial hypertension and proteinuria on rat model of PE [95]. These data suggest that although SIRT1 is required to maintain low expression of sFlt-1, it inhibits sFlt-1 release from cells, and thus SIRT1 activation may be regarded as a therapeutic option in PE patients, along with PPAR γ activation.

3.1.3. Effects of SIRT1 and PPAR γ action towards placentas exposed to oxidative stress

Increased level of oxidative stress has been also found in placentas collected from PE patients [96]. This means an excess of reactive oxygen species (ROS) which may be secondary to hypoxia, ischemia/reperfusion, or reduced level of antioxidants. Since oxidative stress as a possible effect of hypoxia has been already discussed, this paragraph will be focused on other possible causes of oxidative stress. In rat model of maternal malnutrition, diet deficient in folic acid and cobalamin applied in pregnant females results in the increased level of oxidative stress markers in the plasma,

as well as in reduced level of PPAR γ mRNA in the placenta. However, it has no consequences for fetuses or mothers unless placental mass is affected [97]. As to SIRT1, oxidative stress induced by the treatment of human placental explants with hypoxanthine/xanthine oxidase reduces both SIRT1 mRNA and protein expression, as well as inhibits the expression of glucose transporter 1 (GLUT1), a glucose transporter responsible for glucose uptake [12]. These phenotypic alterations can be abrogated by resveratrol [12]. Similarly, treatment with resveratrol reduces oxidative stress in the placenta, as well as apoptosis occurrence in rat model of PE induced with L-NG-nitroarginine methyl ester (L-NAME) [95]. RNA profiling in mouse TSC has identified glutathione peroxidase isoform-encoding genes – GPX1 and GPX2 – as included in ten genes most repressed in SIRT1 KO TSC. GPX protein family accounts for cell protection from oxidative stress through catalyzing the reduction of organic hydroperoxides and hydrogen peroxide with glutathione (GSH) [98]. Reduced expression of GPX1 and GPX3 in SIRT1 KO TSC in comparison to WT TSC has been confirmed with quantitative polymerase chain reaction (qPCR) and correlated with increased apoptosis occurrence in SIRT1 KO TSC. It should be a subject of further evaluation whether SIRT1 KO TSC are indeed more susceptible to oxidative stress because of reduced glutathione peroxidase (GPX) expression. A sum of resveratrol actions as a SIRT1 activator is depicted on **Figure 1**.

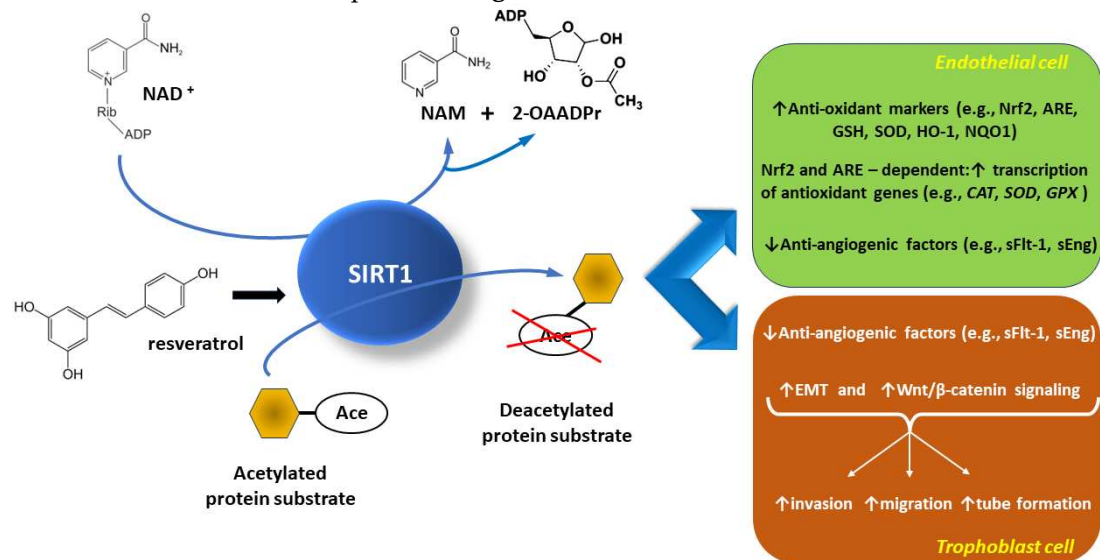


Figure 1. Mechanisms of the beneficial effect of the natural sirtuin-1 activator, resveratrol, at the level of the endothelium and trophoblast under oxidative stress (e.g. accompanying preeclampsia) [7,99–103].

Sirtuin-1 (SIRT1) acts primarily by removing acetyl groups from lysine residues within substrate proteins in the presence of nicotinamide adenine diphosphate (NAD⁺). The NAD⁺ dependence determines that the levels of NAD⁺ and SIRT1 activity (deacetylation) are tightly coupled. The acetyl group is transferred to the 2'-OH position of ADP-ribose, ultimately yielding nicotinamide (NAM) and 2'-O-acetyl-ADP-ribose (2-OAADPr). This oxidative stress-induced epigenetic mechanism reveals/increases the expression of genes that counteract preeclampsia by reducing hypertension, oxidative stress, inflammation and apoptosis in the placenta.

The antihypertensive effect of resveratrol through activation of SIRT1 at the placental level in preeclampsia is mainly based on the inhibition of anti-angiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which are known to cause endothelial and trophoblast dysfunction. In addition, SIRT1 reduces the expression of pro-inflammatory molecules, and increases the expression of anti-oxidant molecules in endothelial cells. Such endothelial antioxidant markers in the preeclamptic placenta are: nuclear factor erythroid 2-related factor 2 (Nrf2), antioxidant response element (ARE), glutathione (GSH), superoxide dismutase (SOD), heme oxygenase-1 (HO-1) and NADPH-quinone oxidoreductase-1 (NQO1). The Nrf2-ARE pathway is an intrinsic mechanism of defense against oxidative stress. Its activation in endothelial cells triggers the transcription of antioxidant genes encoding, among others, catalase (CAT), SOD and glutathione peroxidase (GPX).

Increased SIRT1 activity in the preeclampsia placenta may promote trophoblast cell invasion, migration, and tube formation. This is achieved through activation of epithelial-mesenchymal transition (EMT) and Wnt/ β -catenin pathway. Wnt/ β -catenin signaling, a highly conserved pathway through evolution, regulates key cellular functions including proliferation, differentiation, migration, genetic stability, apoptosis, and stem cell renewal.

3.1.4. Effects of SIRT1 and PPAR γ towards placentas affected by inflammatory response

Inflammatory response within the placenta can occur within the frames of physiology or pathology. An example of physiologic inflammatory response is one observed within the placenta and fetal membranes during a normal delivery. [104]. Such pro-inflammatory conditions at time of delivery have been correlated with unchanged PPAR γ expression accompanied by reduced SIRT1 expression both in fetal membranes and in the placenta [12, 105]. SIRT1 expression in human placenta is regulated by pro-inflammatory cytokines and has been reported to fall after the exposal on interleukins-1 beta (IL-1 β) and TNF- α [12]. Quite interestingly, visfatin/nicotinamide mononucleotide adenylyltransferase (Nampt), an adipokine and SIRT1 activator, positively correlates with SIRT1 activity and its level rises in obese women's placentas just before delivery, which may suggest a possible mechanism preventing SIRT1 activity fall during late pregnancy. It can be sometimes responsible for post-term delivery, commonly observed in obese pregnant women [106].

Pathologic inflammatory response within the placenta is correlated both with PE and maternal obesity [107,108]. In case of microelement deficiency, pronounced inflammation within the placenta has been correlated with reduced expression of PPAR γ mRNA in pregnant female rats [109]. On mouse model of lipopolysaccharide (LPS)-induced intrauterine fetal death (IUFD), preliminary treatment of pregnant mice with PPAR γ activator – rosiglitazone, reduces IUFD occurrence from 64% to 16% [110]. This effect is related to enhanced nuclear location of PPAR γ within placental trophoblast cells, as well as to reduced expression of placental pro-inflammatory mediators, such as interleukin-6 (IL-6) and TNF- α , and abrogating LPS-induced nuclear translocation of PPAR γ within labyrinthine layer of the trophoblast [110]. Finally, on a rat model of LPS-induced PE, a transplant of human mesenchymal stem cells (MSC) results in a reduced activity of pro-inflammatory mediators, such as IL-6 and TNF- α , as well as increased placental PPAR γ activity; this is accompanied by a milder course of arterial hypertension and greater fetal mass in comparison to rats treated with LPS alone [111].

Much less is known about the correlation between obesity-related inflammation within the placenta and SIRT1/PPAR γ expression. This type of inflammation characterizes with T lymphocyte and macrophage infiltration within chorionic villi. This type of inflammation occurs twice more often within placentas of female fetuses, although the reason why is unknown [112]. While macrophage infiltration within adipose tissue has been correlated with reduced SIRT1 expression [113], no alterations in SIRT1 expression have been reported in placentas collected from obese mothers. However, decreased placental SIRT1 expression accompanied by increased placental PPAR γ expression can be observed on mouse model of high fat diet during pregnancy [11]. It has been correlated with increased activity of placental lipoprotein lipase (LPL), as well as with increased adipose tissue content in fetuses, which suggests that maternal overnutrition affects fetal development through altering the activity of SIRT1 and PPAR γ [114]. Dependence of these phenotypic traits on pro-inflammatory mediators has yet to be elucidated. Reduced SIRT1 activity has been reported in mouse WT TSC treated with IL-6 [1], but the way how it is correlated with other markers of trophoblast cell differentiation has not been evaluated.

3.1.5. Correlations between hyperglycemia and placental SIRT1/PPAR γ activity

Although no studies have been conducted on alterations of placental SIRT1 activity in case of maternal diabetes mellitus, similar studies referring to placental PPAR γ activity have shown interesting results. PPAR γ activity has been increased both in human primary trophoblast cells exposed to hyperglycemia [115], and in the placentas of pregnant female mice with streptozotocin-induced diabetes mellitus [116]. On the other hand, many other studies have observed reduced placental PPAR γ expression in case of gestational diabetes mellitus [117–120], and one of those

studies has revealed reduced expression of this protein both in syncytiotrophoblast and in extravillous trophoblast [119]. Further studies are necessary to precisely evaluate the correlation between gestational diabetes mellitus and PPAR γ activity within trophoblast and placenta, taking into consideration both management of maternal hyperglycemia and related effects towards fetal growth.

4. SIRT1-dependent prevention of preeclampsia

4.1. SIRT1 protective actions towards vascular endothelial cells

Endothelial cell dysfunction is one of typical traits of pre-eclampsia, resulting from several factors, including oxidative stress, inflammatory response, autophagy, etc. SIRT1 counteracts oxidative stress, as well as exerts some anti-inflammatory and anti-aging effects. Several research studies have shown that SIRT1 activity is reduced in serum samples collected from PE patients, as well as in human umbilical vein endothelial cells (HUVEC) incubated with such serum [121]. SIRT1 may protect HUVEC from necrosis in PE patients, thus blocking PE development [122]. From the mechanistic point of view, SIRT1 protects endothelial cells from oxidative stress, inflammatory response and cell senescence phenotype through numerous mechanisms, depicted on **Figure 2**.

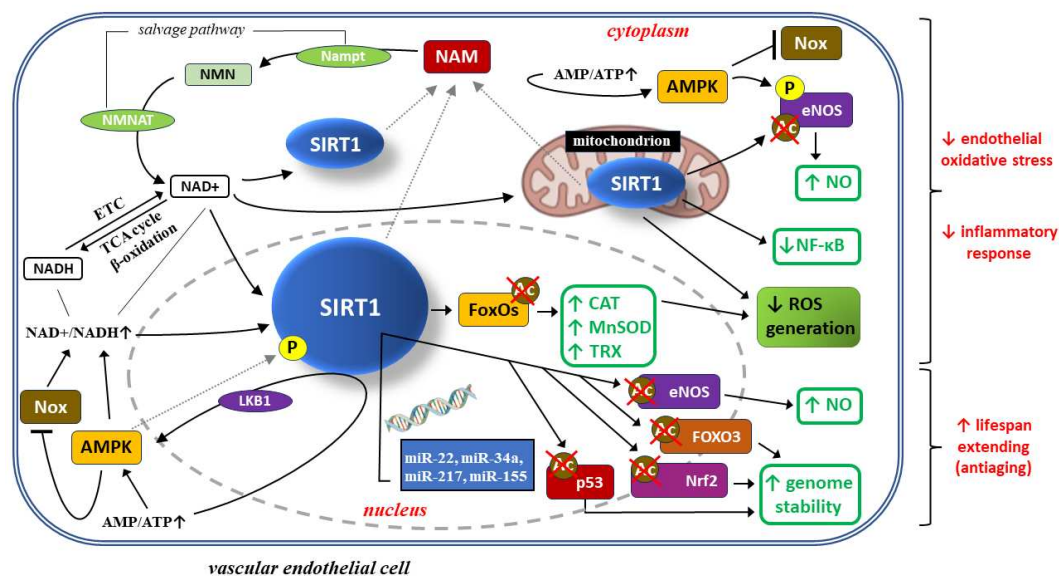


Figure 2. Beneficial effects of SIRT1 on vascular endothelial cells in preeclampsia: limiting oxidative stress, inflammatory response and cellular aging.

SIRT1 (silent information regulator 2 homolog 1) is a crucial cellular survival protein especially in oxidative stress environments. SIRT1 activity depends on oxidized form of nicotinamide adenine dinucleotide (NAD⁺), which is generated from its precursor – nicotinamide mononucleotide (NMN) – by enzyme nicotinamide-(mono)nucleotide adenylyltransferase (NMNAT). Three NMNAT isoforms have been discovered and they show distinct subcellular localizations: NMNAT1 (nucleus), NMNAT2 (cytosol) and NMNAT3 (mitochondria), which suggests a localization-component to NAD⁺ synthesis in response to metabolic signals [123,124]. Similarly, although the main site of SIRT1 synthesis is the nucleus, its activity is also observed in the cytoplasm and mitochondria [123,125]. The level of NAD⁺ is determined by NAD⁺ synthesis from the salvage pathway or NAD⁺ /reduced form (NADH) ratio. Mitochondrial redox metabolism within the electron transport chain (ETC) is crucial for SIRT1 level, because NAD⁺/NADH and AMP/ATP metabolism result from the tricarboxylic acid (TCA) cycle and β -oxidation or oxidative phosphorylation, respectively [126]. NAD⁺ is required in the SIRT1-mediated deacetylase reaction. This reaction also generates nicotinamide (NAM), which then enters the salvage pathway. Nicotinamide mononucleotide adenylyltransferase (Nampt),

catalyzing the conversion from NAM to NMN, is the rate limiting enzyme in this pathway. NMN is thereby converted to NAD⁺ by NMNAT.

The increases in NAD⁺/NADH ratio and AMP/ATP ratio observed during caloric restriction are well-known inducers of SIRT1.

SIRT1 attenuates oxidative stress and inflammation to regulate vascular endothelial functions through several important signal mediators, such as AMP-activated protein kinase (AMPK), nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox), endothelial nitric oxide synthase (eNOS), and forkhead transcription factors of the O class (FOXOs) [7,127]. SIRT1 can stimulate AMPK via the modulation of upstream AMPK kinase such as liver kinase B1 (LKB1), suppressing the production of reactive oxygen species (ROS) and inflammatory response in human umbilical vein endothelial cells (HUVECs), while AMPK influences SIRT1 deacetylation activity by increasing cellular NAD⁺ levels or directly phosphorylating (P) SIRT1. Increased AMP/ATP ratio induces endothelial AMPK, which in turn suppresses Nox expression and Nox-induced ROS production [128]. AMPK-dependent phosphorylation and SIRT1-dependent deacetylation of eNOS lead to an increase in local nitric oxide (NO) concentration. Moreover, SIRT1 deacetylates FoxO proteins, and thus stimulates FoxO-dependent antioxidative enzymes, such as catalase (CAT), manganese superoxide dismutase (MnSOD), and thioredoxin (TRX), eliminating ROS from endothelial cells and thus preventing endothelial dysfunction [127,129,130]. SIRT1 protects endothelial cells from senescence through regulating signaling pathways dependent on tumor protein p53 (p53), eNOS, transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and FOXO3. Expression of these proteins can be in turn regulated at the level of translation by several micro-RNA molecules, such as mi-R217, mi-R34a, mi-R155 and mi-R22 [131–137]. Optimization of NO concentration and genome stability extend the average lifespan of endothelial cells.

4.1.1. SIRT1 and the protection of endothelial cells against oxidative stress and inflammatory response

Oxidative stress and inflammatory response are mutually related pathophysiologic processes taking part in the pathogenesis of PE. Oxidative stress consists in raised concentration of ROS, which results with inflammatory response and – in case of endothelial cells – with their damage and dysfunction [7]. Mitochondrial function is impaired in the course of PE, which results in increased ROS generation, mainly in the form of superoxide anions, causing oxidative stress and systemic inflammation [138–141]. SIRT1 inhibition abrogates the activity of endogenous antioxidative systems on in vitro models of PE. Furthermore, SIRT1 is necessary for counteracting oxidative stress and inflammation in the course of diabetic angiopathy [142–144], while the same two phenomena (i.e. oxidative stress and inflammation) play a crucial role in the pathogenesis of PE. SIRT1 inhibition in hyperglycemic conditions results in endothelial cell dysfunction, while SIRT1 activation alleviates endothelial aging induced by oxidative stress in diabetic mice [145,146]. Quite interestingly, SIRT1 alleviates oxidative stress and inflammatory response through regulating endothelial cell functions via several signaling pathways dependent on adenosine monophosphate(AMP)-activated protein kinase (AMPK), nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox), endothelial nitric oxide synthase (eNOS) and FoxOs [147]. There is a complex network of interactions between AMPK and SIRT1. SIRT1 may activate AMPK through modulation of liver kinase B1 (LKB1) – an upstream regulatory enzyme, modulating AMPK activity [147,148], which inhibits ROS production and inflammatory response in HUVEC. AMPK also affects SIRT1 deacetylase activity through regulation of intracellular NAD⁺ concentration, or directly phosphorylating SIRT1 molecules. In addition, increased activity of NADPH oxidase (Nox) can also increase intracellular NAD⁺ concentration, which stimulates SIRT1 activity in endothelial cells [127]. Moreover, SIRT1 deacetylates FoxO proteins, and thus stimulates FoxO-dependent antioxidative enzymes, such as catalase (CAT), manganese superoxide dismutase (MnSOD), and thioredoxin (TRX), eliminating ROS from endothelial cells and thus preventing endothelial dysfunction [127–130]. SIRT1 has been reported to stimulate c-Myc expression through promoting forkhead box protein O1 (FoxO1) degradation, which prevents hyperglycemia-induced endothelial cell dysfunction and angiogenesis

[149]. eNOS as a nitric oxide synthase (NOS) family protein is expressed in vascular smooth muscle cells and plays a crucial role in the pathogenesis of PE by catalyzing nitric oxide (NO) biosynthesis and at the same time inhibiting ROS production [150]. SIRT1 may directly deacetylate eNOS, or stimulate eNOS activity indirectly, through affecting FoxO proteins and AMPK-dependent signaling pathways [151], which can take part in PE pathogenesis. This evidence suggests that SIRT1 may protect endothelial cells from oxidative stress and inflammatory response through interacting with other enzymes, which can take part in the pathogenesis of PE.

SIRT1 may protect endothelial cells through autophagy regulation

In endothelial cells, autophagy is regulated mainly by SIRT1-dependent and FoxO-dependent signaling pathways, which may take part in the pathogenesis of PE [152]. Research studies have found that SIRT1 activates FoxO₁, thus protecting endothelial cells through autophagy regulation [153]. To be more precise, SIRT1 can deacetylate, and thus activate FoxO₁, while activated FoxO₁ may stimulate SIRT1 expression [154]. FoxO₁ is strictly related to autophagy, since it modulates the expression of such proteins taking part in autophagy as a small GTPase Rab7, LC3, ATG-5, and Beclin-1 [155]. These results suggest that SIRT1 exerts a protective effect on endothelial cells, analogously to the trophoblast (see section 2.2. *Effects of SIRT1 on autophagy within trophoblast*), also by regulating autophagy via multiple signaling pathways, as shown in **Figure 3**.

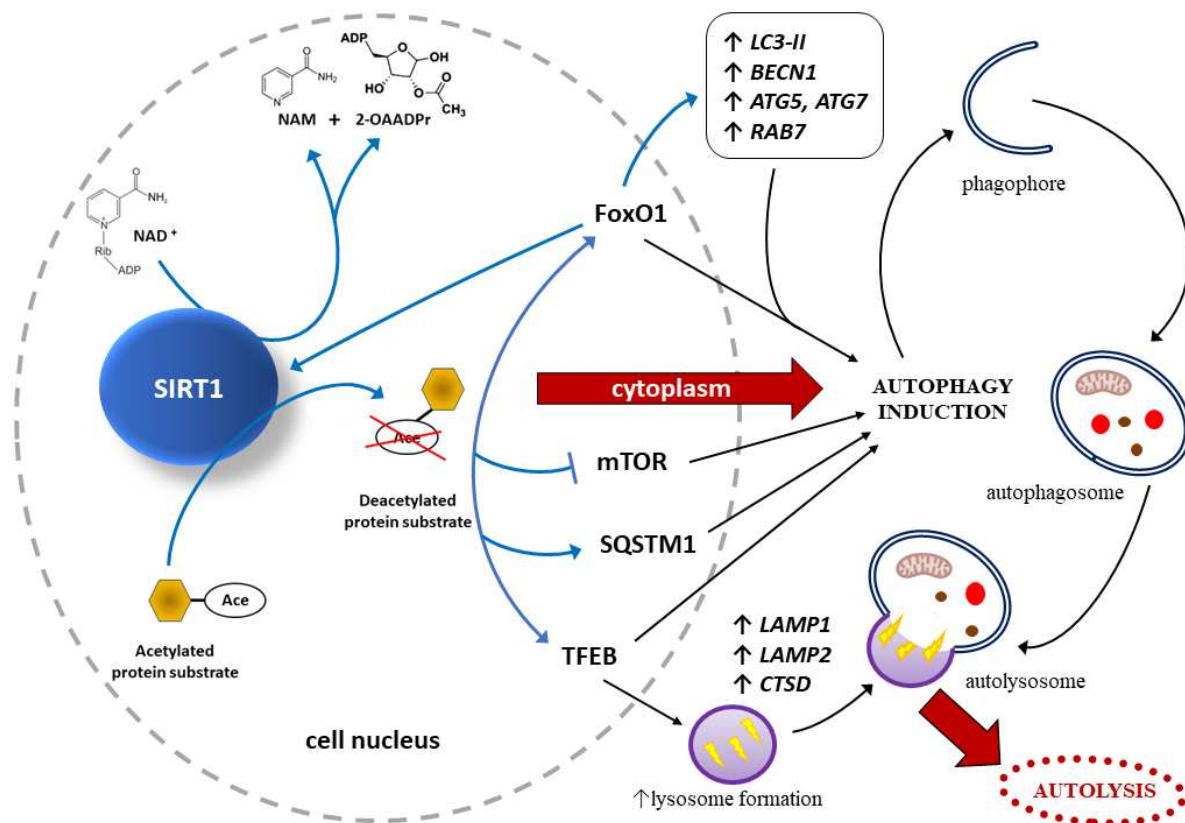


Figure 3. Mechanisms of action of SIRT1 towards maintaining the homeostasis of both endothelial cells and trophoblast by promoting autophagy.

Sirtuin-1 (SIRT1) acts as an energy and redox sensor, because is activated by nicotinamide adenine dinucleotide (NAD⁺), an important substrate in energy and oxidation reactions. As a result of NAD⁺-dependent deacetylation of the respective protein substrates, acetyl groups are transferred to the 2'-OH position of ADP-ribose, ultimately yielding nicotinamide (NAM) and 2'-O-acetyl-ADP-ribose (2-OAADPr) [123,124]. There is an increase in the level of gene expression and, consequently, proteins responsible for the induction and promotion of autophagy, such as forkhead box protein O1 (FoxO₁), sequestosome 1 (SQSTM1, also known as ubiquitin-binding scaffold protein p62), and – a

key regulator of the autophagy/lysosomal-to-nucleus signaling pathway – transcription factor EB (TFEB) [34–37]. Moreover, formation of lysosomes is strictly regulated by TFEB via activation of several downstream autophagy-related genes, such as lysosomal associated membrane protein 1 and 2 (*LAMP1*, *LAMP2*), and cathepsin D (*CTSD*) [32,33].

Sirt1-deacetylated FOXO1 stimulates the expression of *RAB7*, encoding a small GTPase that is a crucial factor in the maturation of autophagosomes and endosomes [156]. Other autophagy-related genes activated directly by SIRT1 or via FoxO1 are those encoding membrane-bound, lipidated form of LC3 (*LC3-II*), a protein containing a Bcl-2 homology-3 domain (*BECN1*), and autophagy related-proteins 5 and 7 (*ATG5*, *ATG7*) [30,31]. In addition, FoxO1 directly activates SIRT1, thus creating an autofeedback loop regulating SIRT1 expression [40]. Autophagy is also induced by SIRT1 inhibiting the mammalian target of rapamycin (mTOR)-related signaling pathway [157,158]. Cell autolysis as a result of autophagy is preceded by the formation of: phagophore, autophagosome and – after fusion of the autophagosome and a lysosome – autolysosome [23–27].

4.1.2. SIRT1 and possible protection of endothelial cells against senescence

CSP occurrence in vascular endothelial cells is a direct cause of most dangerous complications of cardiovascular diseases, and thus most frequent cause of death [159,160]. Quite interestingly, in PE patients CSP has been observed in endothelial progenitor cells, which is related to endothelial dysfunction [161,162]. SIRT1 protects endothelial cells from CSP through regulating some signaling pathways dependent on p53, eNOs, Nrf2, forkhead box protein O3 (FoxO₃), as well as p21/p16. Expression of these proteins can be in turn regulated at the level of translation by several micro-RNA molecules, such as mi-R217, mi-R34a, mi-R155 and mi-R22 [131–137]. Although additional research studies may be required to precisely pinpoint SIRT1 role in endothelial cell senescence phenotype regulation, hitherto performed studies suggest that SIRT1 protects endothelial cells from oxidative stress, inflammatory response, CSP and autophagy through deacetylation of its specific target proteins, which may take part in the pathogenesis of PE.

4.2. Anti-inflammatory action of SIRT1 within the placenta in the context of preeclampsia

SIRT1 plays an essential role in alleviating inflammatory response and oxidative stress in several physiologic and pathologic conditions [163]. Reduced placental SIRT1 expression means that anti-inflammatory and anti-oxidative protection has been compromised. In addition, SIRT1 inhibits high mobility group box 1 (HMGB1) release from cells to the extracellular space, through deacetylation of this non-histone protein molecule. Although in most cases, HMGB1 binds to DNA and promotes transcription of its specific target genes, it is not *sensu stricto* nuclear protein, and its molecules can be translocated to other organelles, or even actively released from cells, which is usually induced by exposure to specific factors (e.g. hypoxia). HMGB1 molecules can also be passively released from cells following cell necrosis [164]. Extracellular HMGB1 activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) through interactions with receptor for advanced glycation end-products (RAGE) and toll-like receptor 4 (TLR4), as well as promotes secretion of pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, and interleukin-8 (IL-8) [164]. Therefore, HMGB1 release to the extracellular environment activates both innate and adaptive immunity. Moreover, some recent research studies suggest that HMGB1 released from hypoxic trophoblast may increase endothelial permeability through signaling pathways dependent on TLR4 and caveolin-1 [165]. Increased permeability of endothelium is the main cause of proteinuria and generalized edemas in the course of PE [165]. HMGB1 concentration in HUVEC-containing medium rises after HUVEC treatment with IL-6 or with serum collected from PE patients, despite reduced HMGB1 concentration in these cells, which suggests that HMGB1 is released from the cells in such conditions. Furthermore, experiments comprising SIRT1 inhibition or activation have shown that SIRT1 may block HMGB1 release from cells on a mouse model of PE, which suggests that SIRT1 can abrogate pro-inflammatory actions of HMGB1 in the course of PE [122]. In addition, SIRT1 inhibits 70-kDa heat shock proteins (HSP70) release from HUVEC after their exposure to IL-6 or serum collected from PE patients. In cells unexposed to stress, HSP70 undergoes a constitutive expression and plays many significant

physiologic roles in almost each organelle, including cytoplasm, endoplasmic reticulum, mitochondria, and cell nucleus [166]. HSP70 expression is induced by several kinds of stress and initially, it has been thought that it helps the cells counteract the stress [166]. However, more recent studies have revealed that HSP70 released to the extracellular environment may bind to many specific signaling receptors, such as lectin-like oxidized low-density lipoprotein-1 (LOX-1), toll-like receptor 2 (TLR2), TLR4, 50-kDa integral membrane protein of the tumor necrosis factor receptor (TNF-R) family (CD40), scavenger receptor expressed by endothelial cell-1 (SREC-1), and link domain-containing scavenger receptor-1 (FEEL-1), which implicates ambiguous effects of HSP70 in some conditions [166]. It has been confirmed that HSP70 activates human monocytes, inhibiting the release of some pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6 and interleukin-10 (IL-10). However, another study has revealed that in patients suffering from early-onset PE, HSP70 concentration in the plasma is positively correlated with concentration of TNF- α , soluble type 1 receptor for TNF- α , IL-1 β , interleukin-12 (IL-12), glutaminoxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase (LDH) and uric acid, which in turn suggests that raised level of HSP70 is related to increased negative effect towards maternal and fetal well-being [166,167]. Molvarec et al. [168] have delivered more evidence suggesting that HSP70 may contribute to systemic inflammatory response in PE patients. They have found serum HSP70 level to be positively correlated with increased levels of such proteins as interleukin-12 subunit beta p40 (IL-12p40), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1). They have also shown that raised levels of HSP70 and sFlt-1/placenta growth factor (PlGF) are independent risk factors of PE development. Although pathogenic functions of HSP70 in PE remain controversial, HUVEC release HSP70 to the extracellular environment in response to stimulation with IL-6 or serum collected from PE patients, which suggests that they perceive such stimulation as a kind of stress. Forced expression of SIRT1 inhibits HSP70 release from cells, which indicates that it may inhibit HUVEC response to stress in the course of PE. One recent research study has shown that SIRT1 indeed affects HSP70 expression in cells. Inducible HSP70 has been shown to be upregulated in spinal cord of mice chronically overexpressing SIRT1 in the central nervous system [169]. Studies on SIRT1 mechanisms of action indicate that it deacetylates heat shock transcription factor 1 (HSF-1) transcription factor that is an essential regulator of heat shock proteins (HSPs) expression, which results in enhanced expression of inducible HSP70 [169]. Few studies, however, deals with SIRT1 role in modulating HSP70 release from cells. Those studies which have explored this issue may deliver a first piece of evidence that SIRT1 can inhibit HSP70 release from HUVEC cells, thus counteracting the effects of exposure to IL-6 or serum collected from PE patients. However, further studies are necessary to pinpoint the mechanisms through which SIRT1 modulates HSP70 release from cells. In the course of PE, excessive inflammatory response and oxidative stress result in endothelial cell damage and death. Necrotic cells may release HMGB1, which can further enhance inflammatory response, resulting in a vicious circle. SIRT1 protects HUVEC from necrosis resulting from their exposure to IL-6 or serum collected from PE patients. This protective effect of SIRT1 is probably related to its anti-inflammatory and anti-oxidative actions, but also to its anti-apoptotic functions. Many studies have confirmed that SIRT1 can deacetylate p53, thus abrogating its proapoptotic actions [170]. Furthermore, SIRT1 has been found to be downregulated in the placentas of PE model mice, while HMGB1 and HSP70 serum concentrations are markedly elevated in such mice. SIRT1 inhibits HMGB1 and HSP70 release from HUVEC exposed to IL-6 or serum collected from PE patients and protects the cells from necrosis. All these findings indicate that SIRT1 can play a protective role in PE, alleviating its manifestations.

SIRT1 alleviates PE course on animal models of PE

SIRT1 activity is reduced both in PE patients' placentas and sera and in placentas and sera collected from mice used as an animal model of PE [171]. It has been found that SIRT1 inhibition in SIRT1^{-/-} mice induces typical manifestations of PE, such as arterial hypertension, proteinuria, intrauterine growth retardation, renal damage, as well as labyrinthine layer atrophy. Moreover, all of these manifestations can be alleviated by the treatment with experimental drug SRT2104, a potent

SIRT1 inducer [22]. It has also been reported that SIRT1 KO mice placentas and fetuses show abnormalities both within labyrinthine layer and in junctional zone. In addition, SIRT1 KO mice develop numerous abnormalities, from increased prenatal mortality to fetal growth impairment resulting in greater postnatal mortality [172–175]. Furthermore, placentas collected from SIRT1 KO mice show increased occurrence of cell senescence phenotype, as well as other morphologic abnormalities [176], which is strictly correlated with PE development.

SIRT1 induction alleviates PE manifestations

In reduced uterine perfusion pressure (RUPP) rats, constituting an animal model of PE, supplementation with recombinant SIRT1 protein alleviates PE manifestations, such as arterial hypertension, impaired placental angiogenesis, inflammatory response, and unfavorable pregnancy outcome [177]. Similar effect may be achieved through treatment with SIRT1 inducer – SRT2104 [22]. However, more animal studies and clinical trials are needed to precisely determine SIRT1 role in PE.

5. Conclusion

Recently, there have been more and more publications on the activity of sirtuins in placental tissue in normal and complicated pregnancies. This applies in particular to SIRT1 in placental vascular endothelial cells and trophoblast cells. [8,178–181]. Directly involved in many key intracellular reactions, SIRT1 builds up the connection between epigenetics and metabolism at the placental level [182]. As an NAD⁺-dependent deacetylase, SIRT1 regulates many aspects of chromatin biology, such as transcription, recombination, and genome stability, by modifying histones, transcription factors, and epigenetic enzymes, and in connection with the above, it directly affects placental homeostasis by modifying a diverse set of metabolic enzymes, both in the cytosol and in the mitochondria [1,183]. The beneficial effects of SIRT1 in the human placenta known so far relate primarily to modulating the activity of factors responsible for the course of the inflammatory response, oxidative stress, autophagy, and cell senescence [7,29,155,184–187].

Therefore, there are well-documented reasons to treat the activation or inhibition of SIRT1 as a potential therapeutic target, especially in hypertensive disorders complicating pregnancy, in which the main pathomechanism is based on endothelial dysfunction [5,7,8,188]. This is even more important as the incidence of PE is increasing, possibly as a result of increased prevalence of predisposing disorders, such as chronic hypertension, diabetes, and obesity [189,190].

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Abbreviations

2-OAADPr – 2'-O-acetyl-adenosine diphosphate(ADP)-ribose.

AMPK – adenosine monophosphate(AMP)-activated protein kinase.

ARE – antioxidant response element.

ATG5: ATG7, ATG8 – autophagy related-proteins 5, 7, 8.

Beclin-1 – the mammalian ortholog of yeast Atg6/Vps30, an essential autophagy protein that contains a Bcl-2 homology-3 domain.

BECN1 – Beclin-1 gene.

CAT: CAT – catalase gene, catalase (antioxidant enzyme), respectively.

CD40 – 50-kDa integral membrane protein of the tumor necrosis factor receptor (TNF-R) family.

CSP – cell senescence phenotype.

CTSD – cathepsin D .

EMT – epithelial-mesenchymal transition.

eNOS – endothelial nitric oxide synthase.

ETC – electron transport chain.

FEEL-1 – link domain-containing scavenger receptor-1.

FoxOs – forkhead O class box transcription factors.

FoxO1: FoxO3 – forkhead box protein O1 and O3, respectively.

GCM1 – glial cells missing-1 (transcription factor).

GLUT1 – glucose transporter 1.

GOT – glutamicoxaloacetic transaminase.

GPT – glutamic pyruvic transaminase.

GPX – glutathione peroxidase.

GPX1: GPX2, GPX3 – glutathione peroxidase isoforms 1, 2 and 3, respectively.

GSH – glutathione.

H₂O₂ – hydrogen peroxide.

HIF – hypoxia-inducible factor (HIF).

HIF-1 α – hypoxia-inducible factor 1 subunit alpha.

HIF-2 α – hypoxia-inducible factor 2 subunit alpha.

HIF α : HIF β – domains that make up the (hypoxia-inducible factor) HIF molecule domain.

HMGB1 – high mobility group box 1 (nonhistone nuclear protein).

HO-1 – heme oxygenase-1.

HSF1 – heat shock transcription factor 1.

HSP70 – 70-kDa heat shock proteins.

HSPs – heat shock proteins.

HUVEC – human umbilical vein endothelial cells.

ICAM-1 – intercellular adhesion molecule 1, also known as CD54 (cluster of differentiation 54).

IL-1: IL-1 β , IL-6, IL-8, IL-10, IL-12 – interleukins: 1, 1 beta, 6, 8, 10 and 12.

IUFD – intrauterine fetal death.

IL-12p40 – interleukin-12 subunit beta (p40).

KO – knockout.

L-NAME – L-NG-nitroarginine methyl ester.

LAMP1: LAMP2 – lysosomal associated membrane protein 1,2.

LC3 – microtubule-associated protein 1 light chain 3 (MAP1LC3), a human homologue of yeast Atg8, an essential component of autophagy.

LC3-II – membrane-bound: lipidated form of LC3.

LDH – lactate dehydrogenase.

LKB1 – liver kinase B1.

LOX-1 – lectin-like oxidized low-density lipoprotein-1.

LPL – placental lipoprotein lipase.

LPS – lipopolysaccharide.

MCP-1 – monocyte chemoattractant protein-1.

mi-R217: mi-R34a, mi-R155, mi-R22 – micro-RNA molecules.

MnSOD – manganese superoxide dismutase (antioxidant enzyme).

mTOR – mammalian target of rapamycin (an ubiquitous serine-threonine protein kinase).

NAD – nicotinamide adenine dinucleotide.

NAD⁺ – nicotinamide adenine dinucleotide (oxidized form).

NADH – nicotinamide adenine dinucleotide (reduced form, H for hydrogen).

NAM – nicotinamide.

NCoR1 – nuclear receptor co-repressor-1.

NDRG1 – N-myc downstream regulated gene 1 (formerly known as *Drg1*, *Cap43*, *Rit42*, *RTP*, and *PROXY-1*).

Nampt – nicotinamide mononucleotide adenylyltransferase.

NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells.

NMN – nicotinamide mononucleotide.

NMNAT – nicotinamide-(mono)nucleotide adenylyltransferase.

NMNAT1: NMNAT2, NMNAT3 – nicotinamide-(mono)nucleotide adenylyltransferase isoforms: 1,2, and 3.

NO – nitric oxide.

NOS – nitric oxide synthase.

Nox – nicotinamide adenine dinucleotide phosphate (NADPH) oxidases.

NQO1 – nicotinamide adenine dinucleotide phosphate (NADPH)-quinone oxidoreductase-1.

Nrf2 – nuclear factor erythroid 2-related factor 2.

p62 – ubiquitin-binding scaffold protein, also known as sequestosome 1 (SQSTM1).

p53 – protein encoded by the *TP53* tumor suppressor gene, marker of cell senescence.

p21 – cyclin-dependent kinase inhibitor p21, protein marker of cell senescence.

PE – preeclampsia.

PlGF – placenta growth factor.

PPARγ – peroxisome proliferator-activated receptor γ.

PPARγ2 – an isoform of PPARγ typical for adipose tissue.

PPRE – PPARγ-reactive elements.

PRDM1 – positive regulatory (PR) domain zinc finger protein 1, a coactivator selectively activating PPARγ.

Prdm16 – positive regulatory domain containing 16.

qPCR – quantitative polymerase chain reaction.

Rab7 – a small GTPase: member of the Rab family that controls transport to late endocytic compartments such as late endosomes and lysosomes.

RAB7 – Rab7 gene.

RAGE – receptor for advanced glycation end-products .

ROS – reactive oxygen species.

RUPP – reduced uterine perfusion pressure.

RXR – retinoid X-receptor.

SASP – senescence-associated secretory phenotype.

sEng – soluble endoglin: the extracellular domain of membrane endoglin.

sFlt-1 – soluble fms-like tyrosine kinase 1, also known as soluble vascular endothelial growth factor (VEGF) receptor-1 .

siRNA – small interfering RNA.

SIRT1 – silent information regulator 2 homolog 1 or sirtuin-1.

SIRT1 – SIRT7 – sirtuins 1 to 7 .

SMAD2: SMAD3 – small mothers against decapentaplegic proteins 2 and 3 (transcription factors).

SMRT – silencing mediator of retinoid and thyroid hormone receptors.

SOD – superoxide dismutase.

SQSTM1 – sequestosome 1: also known as ubiquitin-binding scaffold protein p62.

SREC-1 – scavenger receptor expressed by endothelial cell-1.

SRT2104 – experimental drug, a selective small molecule activator of SIRT1.

STAT – signal transducer and activator of transcription (transcription factor).

STAT3 – signal transducer and activator of transcription 3 (transcription factor).

TCA – tricarboxylic acid cycle, also known as the Krebs cycle or the citric acid cycle.

TFEB – transcription factor EB (TFEB), a member of the MiT/TFE family of basic helix-loop-helix leucine zipper transcription factors, a key regulator of the autophagy/lysosomal-to-nucleus signaling pathway.

TLR2: TLR4 – toll-like receptor 2 and 4.

TNF- α – tumor necrosis factor alpha.

TRX – thioredoxin (antioxidant protein).

TSC – trophoblast stem cells.

TZD – thiazolidinediones: synthetic activators of PPAR γ .

WT TSC – wild-type trophoblast stem cells (TSC).

VCAM-1 – vascular cell adhesion molecule 1, also known as CD106 (cluster of differentiation 106).

VEGF – vascular endothelial growth factor.

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