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REVIEW

Hypoxia: Role of SIRT1 and the protective effect of resveratrol in ovarian function

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Abstract

Background: Ovarian function is closely related to the degree of vascular network development surrounding the ovary. Maternal aging-related construction defects in this vascular network can cause ovarian hypoxia, which impedes oocyte nutrient supply, leading to physiological changes in the ovaries and oocytes. The anti-aging gene Sirtuin 1 (SIRT1) senses and adapts to ambient stress and is associated with hypoxic environments and mitochondrial biogenesis.

Methods: The present study is a literature review focusing on investigations involving the changes in SIRT1 and mitochondrial expression during hypoxia and the cytoprotective effects of the SIRT1 activator, resveratrol.

Main findings: Hypoxia suppresses SIRT1 and mitochondrial expression. Resveratrol can reverse the hypoxia-induced decrease in mitochondrial and SIRT1 activity. Resveratrol suppresses the production of hypoxia-inducible factor-1α and vascular endothelial growth factor proteins.

Conclusion: Resveratrol exhibits protective activity against hypoxic stress and may prevent hypoxia- or aging-related mitochondrial dysfunction. Resveratrol treatment may be a potential option for infertility therapy.

KEYWORDS
aging, hypoxia, mitochondria, resveratrol, sirtuin 1

1 | INTRODUCTION

Angiogenesis is a critical process during folliculogenesis, ovulation, and corpus luteum formation in the human ovary.[1-5] Ovarian follicular microvasculature development is regulated by angiogenic factors, including the hepatocyte growth factor, angiopoietin, and members of the vascular endothelial growth factor (VEGF) family and the CXC chemokine family.[6-14] Ovarian function is closely related to the degree of ovarian tissue vascular network development. Maternal age-related defects in the construction of the vascular network surrounding the ovary can lead to ovarian hypoxia, which is assumed to affect ovarian follicle growth and development. Hypoxia and the aneuploid oocyte increase associated with advanced reproductive age can also result from age-related dominant follicle microvasculature deficiencies.[10,15]

Mitochondrial quantity is highly positively correlated with oocyte maturation and fertilization and the subsequent embryo development.[16-19] Cellular hypoxia substantially suppresses mitochondrial gene expression, and the mitochondria count reduction caused by aging and hypoxia may be the primary source of infertility in advanced age animals.[20-23]

Sirtuin-1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase, detects and adapts to ambient stress.[24-26] SIRT1 is activated by caloric restriction and natural

polyphenolic compounds such as resveratrol[27-31] and is involved in the regulation of various cellular physiological and pathological processes, including gene silencing, stress resistance, apoptosis, and inflammation, all of which are associated with aging-related diseases.[32-35] SIRT1 activity is primarily nuclear but significantly impacts mitochondrial biogenesis and turnover.[23,36,37,38,39,40,41] Recent studies have demonstrated that SIRT1 promotes mitochondrial biogenesis via deacetylation of target proteins such as peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α and hypoxia-inducible factor (HIF)-1α, indicating potential therapeutic benefits of SIRT1 activation in metabolic and other aging-related diseases.[36,42,43]

To further elucidate the molecular and cellular mechanisms involved in the role of SIRT1 in hypoxia, we focused this review on the changes in both SIRT1 and mitochondrial expression during hypoxia and the protective effects of resveratrol. Furthermore, we present possible remediation measures for ovarian hypoxia.

2 | SIRT1 AND OVARIAN FUNCTION

2.1 | SIRT1

Sirtuins are protein members of the class III NAD^+-dependent histone deacetylase family, or the silent information regulator 2 family. Because changes in the NAD^+/NADH ratio regulate sirtuin activity, all members of this family may play crucial roles in the detection of cellular energy status.[27,44] To date, seven members of the sirtuin family, SIRT1–7, have been identified in mammals, with each member exhibiting unique subcellular localization, function, and substrate specificity.[45,46] SIRT1 and SIRT2 have been found in both the nucleus and cytosol, SIRT3, SIRT4, and SIRT5, exclusively in mitochondria, and SIRT6 and SIRT7, exclusively in the nuclear compartment.[47-49] The presence of all sirtuins has been confirmed in granulosa cells (GCs) and human ovarian granulosa-like tumor (KGN) cells.[50]

Among the sirtuins, SIRT1 is the most phylogenetically similar to yeast Sir2, the most prominent, and the most extensively studied.[51] Chiefly located in the nucleus, with some environmental signal-triggered shuttling to the cytosol, SIRT1 has the capability to extend lifespan, delay aging, and prevent aging-related diseases, primarily via catalysis of histone deacetylation and regulation of transcription factors or coactivators, such as p53, forkhead box O (FOXO), nuclear factor-κB (NF-κB), PGC-1α, and Ku70.[52-54] It is involved in the regulation of biological and pathological processes, such as apoptosis via inhibition of p53-dependent transcription, inflammation via reduction of NF-κB activity, and energy metabolism via regulation of metabolic enzymes like PPAR-γ.[32,55,56,57,58,59] The SIRT1 preventative mechanisms in aging and aging-related diseases are likely diverse and dependent on the regulated proteins. In addition, SIRT1 endogenous levels are related to aging-related disease development.[60] Besides affecting the protein levels of SIRT1, aging also impacts its activity.[61] Age-dependent decrease in the level of SIRT1 is observed in the brain, liver, muscle, and arteries.[62-66] SIRT1 deficiency promotes the expression of genes characteristic of aging.[67]

SIRT1 is expressed not only in GCs and cumulus cells but also in oocytes and theca cells.[65,68,69,70] In the reproductive system, *SIRT1* plays a role in GC apoptosis during follicular atresia, has been linked to follicular reserve preservation and ovarian lifespan extension, and is an essential factor in the activation of the steroidogenesis associated with luteinization and terminal differentiation.[68,71,72]

2.2 | Resveratrol

Numerous studies have explored controlling sirtuin-dependent downstream pathways via pharmacological- and nonpharmacological-based sirtuin activation. Resveratrol (3,5,4′-hydroxystilbene), a natural polyphenolic compound commonly found in grapes, berries, red wine, and several botanical extracts, was one of the first compounds recognized as a SIRT activator.[30,73] Resveratrol has a chemical structure similar to that of some estrogens, such as diethylstilbestrol, and is considered a natural phytoestrogen.[74,75] As the most potent natural SIRT1 ligand, resveratrol has received a great deal of attention due to its beneficial anti-oxidant, anti-inflammatory, anti-aging, anti-carcinogenic, and anti-angiogenic qualities.[76-81] Stressful events induce SIRT1 activation and binding to various molecular targets, including NF-κB, tumor protein p53, FOXO, PGC-1α, liver X receptor, and HIF-2α.[25,49] By activating these molecules via SIRT1, resveratrol plays a pivotal role in energy homeostasis regulation, gene silencing, genomic stability, and cell survival. Resveratrol has been found to extend the lifespan of *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, and *Drosophila melanogaster*, and increase energy metabolism and mitochondrial oxidative capacity.[82]

2.3 | Effect of resveratrol on GCs and oocyte via SIRT1

Sirtuin expression has been detected in mammalian ovaries, GCs, oocytes, and embryos.[65,68,69,70,83] Resveratrol may provide protection against ovarian aging through SIRT1-related cellular mechanisms, via an anti-oxidative effect, protecting oocytes from age-dependent defects.[44]

Various studies have reported the effects of resveratrol, such as increased ATP production and the promotion of mitochondrial biogenesis, on mammalian—including human—GCs.[84] In rat GCs, resveratrol treatment induces transcription-level upregulation of SIRT1, the luteinizing hormone receptor, the steroidogenic acute regulatory protein, and P450 aromatase, but does not affect the regulation of the follicle-stimulating hormone receptor, suggesting that resveratrol and SIRT1 can modulate ovarian functions via folliculogenesis-related molecule and gonadotropin receptor activation.[68]

In swine GCs, resveratrol increases SIRT1 mRNA and protein levels in a dose-dependent manner, accelerating cell apoptosis, and follicular atresia.[71] Resveratrol supplementation of cultured

porcine ovarian GCs increases SIRT1 protein levels, induces apoptosis, promotes testosterone and estrogen release, and inhibits cell proliferation.[85]

Interestingly, resveratrol treatment also promotes mitochondrial synthesis, ATP production, and autophagy in GCs from advanced age cows, improving mitochondrial function and in vitro oocyte development.[86] Improved regulation of GC function is an expected result of stimulation of mitochondrial biogenesis by resveratrol. Resveratrol supplementation of maturation medium enhances SIRT1 protein expression and increases the ATP content in bovine oocytes, resulting in improved fertilization outcomes.[87] In human oocytes, resveratrol increases the emission rate of first polar body and reduces the percentage of spindle with abnormal morphology.[88] These reports on the impact of resveratrol on GCs correlate with current evidence for the overall effect exerted by resveratrol on ovarian physiology and with the results of a recent study suggesting that mitochondrial function in cumulus cells and GCs can directly influence pregnancy outcomes.[89-91]

These findings led us to investigate the direct impact of hypoxia and resveratrol on the SIRT1/PGC-1α pathway and on the quantity of mitochondria in KGN cells (Figure 1A–F).[92] Resveratrol significantly and dose-dependently upregulates, whereas hypoxic stress induced by cobalt chloride ($CoCl_2$, a hypoxia-mimicking agent) significantly downregulates the expression of SIRT1, PGC-1α, and mitochondrial DNA (mtDNA) in comparison to the controls.

To further examine the protective effect of resveratrol from $CoCl_2$-induced hypoxic stress, KGN cells were cultured in medium containing 100 μmol/l $CoCl_2$, with or without 50 μM resveratrol. $CoCl_2$-induced hypoxic stress resulted in the downregulation of the expression of SIRT1 and PGC-1α, and reduced mtDNA copy number, and resveratrol reversed the $CoCl_2$-induced inhibitory effects of hypoxia.

The cumulative results indicate that upregulation of SIRT1 by resveratrol partially improves the condition of hypoxiated GCs by increasing mitochondria quantity. Thus, resveratrol may have a potentially beneficial effect in ameliorating reproductive function via SIRT1 regulation.

2.4 | SIRT1 activators other than resveratrol

Several SIRT1 activators other than resveratrol have been reported to improve reproductive function. They have also been reported to improve reproductive function. Melatonin protects premature ovarian insufficiency by reducing oxidative stress and apoptotic damage via activation of SIRT1 signaling in a receptor-dependent manner in rats.[93] N-acetyl-L-cysteine treatment has been demonstrated to increase the quality of the oocytes from old mice in association with the higher expression level of Sirt1 and Sirt2, and increased telomerase activity and length.[94] On the contrary, it was demonstrated that an inhibitor of SIRT1 increased the ratio of abnormal fertilization.[95] Thus, SIRT1 is clearly involved in the protection of ovarian function.

2.5 | Clinical studies with resveratrol

Surprisingly, resveratrol has been reported to have a negative effect on pregnancy outcomes. Ochiai et al. demonstrated that women with regular resveratrol supplementation (200 mg/day) during IVF–embryo transfer cycles had lower pregnancy rates and higher miscarriage rates. Resveratrol has potential therapeutic effects in improving ovarian function; however, it also has anti-deciduogenic activity. Therefore, it is recommended to avoid the consumption of the compound during the luteal and gestational phases.[96] Initial clinical applications of resveratrol have taken into account its various positive and negative effects.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age and is primarily characterized by hyperandrogenism and ovulatory dysfunction.[97] The effect of resveratrol on the endocrine and metabolic functions of PCOS patients was evaluated during a 3-month placebo-controlled randomized clinical trial. This study revealed that resveratrol (1500 mg/day p.o.) reduces the levels of serum testosterone, serum dehydroepiandrosterone sulfate, and insulin, while increasing the insulin sensitivity index. Improvement in hyperandrogenemia observed in response to resveratrol was comparable to, or greater than, that observed in response to metformin, an effect possibly related to improvements in insulin sensitivity and level.[98]

The impact of resveratrol on the management of endometriosis-related pain was investigated in a clinical trial involving 12 patients of reproductive age (range 22–37 years), with a laparoscopic diagnosis of endometriosis, who had failed to obtain pain relief using an oral contraceptive containing drospirenone +ethinylestradiol alone for 6 months. The addition of 30 mg of resveratrol to the contraceptive regimen resulted in a significant reduction in pain scores, with 82% of patients reporting complete resolution of dysmenorrhea and pelvic pain after 2 months of use. These results demonstrate that resveratrol potentiates the efficacy of oral contraceptives in the management of endometriosis-associated dysmenorrhea.[99]

Although most studies that have revealed the excellent anticancer properties of resveratrol have been performed in cell culture and pre-clinical models, a small number of clinical trials involving cancer patients have been reported.[100] In addition to the effects in subjects with cancer, the effect of resveratrol in subjects with a higher cancer risk has also been demonstrated. A pilot study was conducted in postmenopausal women with a high body mass index (BMI ≥25 kg/m^2) to determine the clinical effect of resveratrol on systemic steroid hormones. A 12-week 1 g/day resveratrol supplementation has been shown to increase the concentration of sex steroid hormone-binding globulin, a protein that has been linked to reduction in breast cancer risk, and resulted in an average of 73% increase in urinary 2-hydroxyestrone (2-OHE1) levels leading to a favorable change in urinary 2-OHE1/16α-OHE1 ratio.[101] The results indicate that resveratrol supplementation has a favorable influence on estrogen metabolism and lowered breast cancer risk factors in obese and overweight postmenopausal women.[102] Therefore, resveratrol has provided some benefit in cancer prevention and

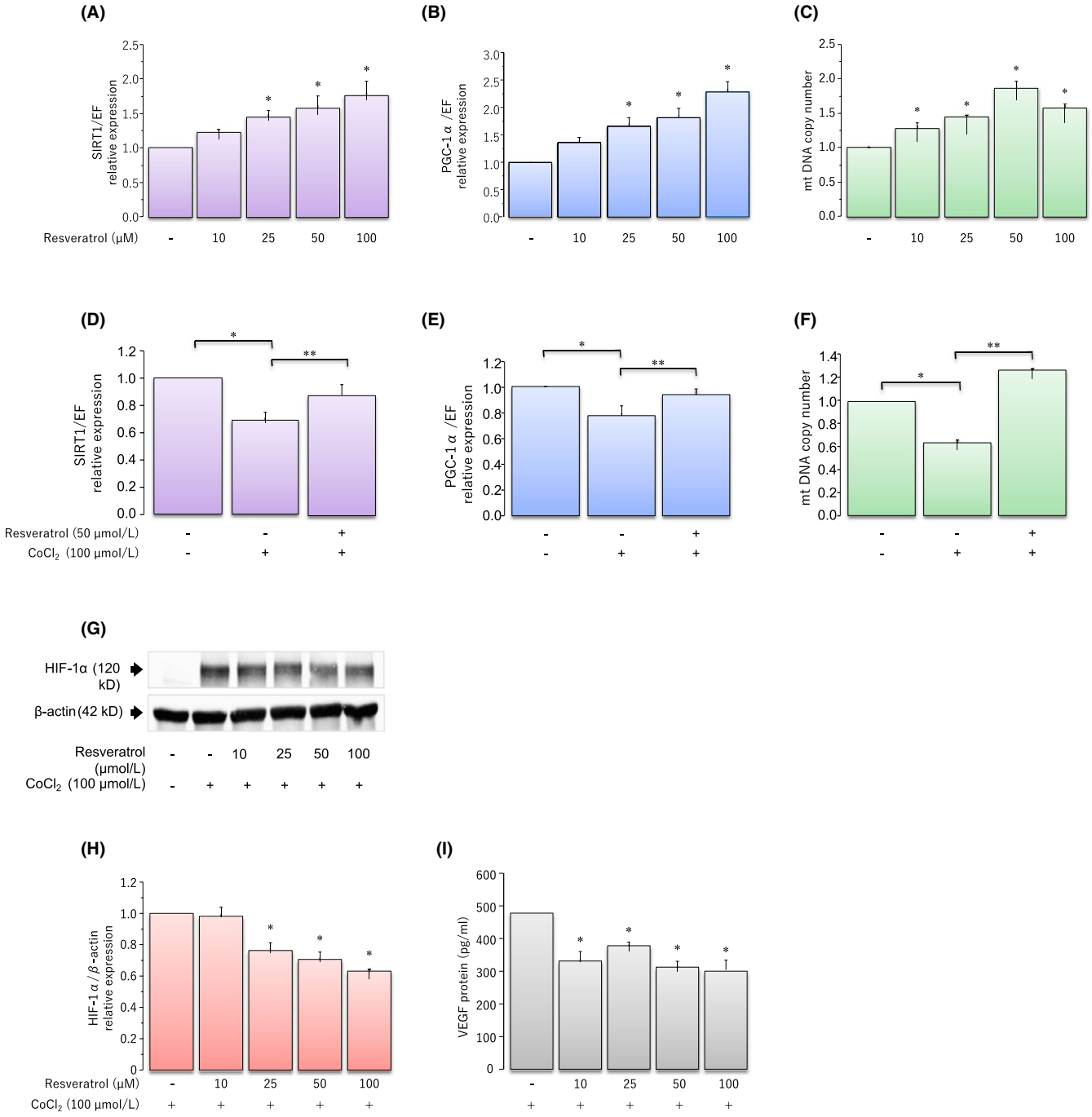

FIGURE 1 Protective effects of resveratrol during $CoCl_2$-induced hypoxic stress. Effects of various concentrations of the resveratrol on KGN cells. (A) Sirtuin 1 (SIRT1) mRNA and (B) peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α mRNA levels were assessed via real-time PCR and calculated after normalization to elongation factor 1α mRNA levels. (C) Mitochondrial DNA copy number was determined via real-time PCR. Effects of $CoCl_2$-induced hypoxic stress on mRNA expression and protein secretion. (D) SIRT1 mRNA and (E) PGC-1α mRNA levels were assessed via real-time PCR and calculated after normalization to elongation factor 1α mRNA levels. (F) Mitochondrial DNA copy number was determined via real-time PCR. (G) The expression of hypoxia-inducible factor (HIF)-1α was quantified using western blotting. The levels of HIF-1α were normalized to β-actin levels. (H) The protein levels were quantified using ImageJ. (I) Levels of vascular endothelial growth factor protein were analyzed via enzyme-linked immunosorbent assay. Fold differences are shown in comparison with the control, for which the value was defined as 1.0. Data are presented as mean ±SEM, n = 3. Statistically significant differences are indicated in brackets: * $p < 0.05$ versus the control group; ** $p < 0.05$ versus the 100 μmol/L $CoCl_2$ treatment group. These figures have been modified from Nishigaki et al.[92] *Reprod Med Biol*. 2020

treatment, and the efficacy and safety of resveratrol in human trials must be further investigated to better understand and develop its therapeutic potential.

At present, clinical trials of resveratrol have been limited due to unresolved issues, such as its extensive metabolism leading to poor bioavailability and its adverse side effects, including diarrhea, nausea, and abdominal pain.[103,104]

3 | HYPOXIA AND OVARIAN FUNCTION

3.1 | HIF-1α expression during hypoxia

Hypoxia potentially contributes to aging-related functional decline, and reducing hypoxic damage and senescence induction requires improved understanding of the molecular and cellular responses to hypoxia.[21] An appropriate response to changes in oxygen availability, particularly coping with oxygen deficiency in hypoxic environments, is essential for survival.

Cellular level hypoxic responses are largely mediated by HIFs, which act as transcriptional regulators of the genes involved in survival during periods of low oxygen and are regulated primarily by oxygen-dependent proteasomal degradation. HIF-1α is stably expressed during hypoxia.[105-107]

One such contribution involves VEGF, a 46-kDa disulfide-linked homodimeric glycoprotein that stimulates vascular endothelial cell proliferation, migration, tubule organization, and permeability.[108] Repeated evidence has demonstrated that VEGF production is regulated by HIF-1α, particularly under hypoxic conditions.[109] During hypoxia-stimulated angiogenesis, HIF-1 transcriptionally regulates VEGF expression by directly binding to the hypoxia-response elements in the VEGF promoter.[110,111] Recent studies have demonstrated that VEGF is an essential regulator of ovarian angiogenesis, a critical process in follicular development and corpus lutea formation.[108,112] In addition, both hypoxia and $CoCl_2$ have been reported to induce VEGF production in ovarian GCs.[10] VEGF acts as a key angiogenic factor in ovarian vascularization regulation and may play a modulatory role in GC functional activity and follicular growth.

As a follicle grows, follicular fluid oxygen concentration decreases, causing the accumulation of HIF-1α, which is speculated to promote VEGF transcription and angiogenesis around the follicle. HIF-1α, which is involved in follicle development and luteinization in the ovaries of mammals, including those of humans, is expressed in human corpus luteum and luteinized GCs. Hypoxia increases VEGF directly, and nuclear HIF-1α is most active in the early luteal phase at the time of maximal angiogenesis.[113]

Aging contributes to ovarian hypoxic stress, which affects ovarian follicle growth and development. Aging-related hormonal imbalances cause non-optimal microvasculature to develop around maturing and mature follicles. The resulting reduction in perifollicular capillary bed size and blood flow through the area leads to an oxygen deficit and the concomitant accumulation of carbon dioxide and anaerobic products, such as lactic acid, inside the follicle. The consequent decrease in oocyte intracellular pH diminishes the spindle size, causing chromosome displacement and nondisjunction.[15]

Higher follicular fluid VEGF concentrations have been reported to correlate positively with female age.[10] Thus, aging-associated deficient microvasculature around the dominant follicle results in hypoxia, and the predisposition toward increased aneuploid oocyte incidence is associated with advanced reproductive age.

Mitochondria are multifunctional organelles essential to energy production, apoptosis, and calcium homeostasis,[114,115] and their quantity is closely related to oocyte maturation, fertilization, and subsequent development.[16-19] Cellular hypoxia significantly suppresses mitochondrial gene expression,[21] and the reduction in mitochondrial quantity due to aging and hypoxia may be the primary cause of infertility in advanced age animals.[16,23,116] Therefore, HIF-1α regulation mechanisms have been implicated in the prevention of premature cellular senescence and the pathogenesis of numerous aging-related chronic diseases.

Recent reports have suggested an important connection between HIF-1α and SIRT1.[26,117,118] Lim et al. observed that SIRT1 interacts with HIF-1α in multiple cell lines and mouse tissues, and modulates cellular hypoxia responses via HIF-1α deacetylation.[26]

3.2 | SIRT1, a key regulator of hypoxic stress

During hypoxia, expression of *SIRT1* is suppressed, whereas that of HIF-1α is activated.[21,118] At least two distinct mechanisms have been suggested of the former effect: reduced transcription of *SIRT1* mRNA and a decrease in the NAD^+/NADH ratio.[119,120] The ratio of NAD^+, a SIRT-mediated deacetylation substrate, to NADH is an important physiological regulator of SIRT activity, and intracellular levels of both are modulated by nutrient deprivation, energy consumption, or hypoxia.[49]

During hypoxia, decreased NAD^+ levels downregulate SIRT1 activity, which leads to increased HIF-1α acetylation and enhanced induction of hypoxic response genes, implying that crosstalk between hypoxia and metabolism detection pathways ensures cellular adaptation to hypoxia.[26] In addition, HIF-1α is inactivated by SIRT1 activators, such as resveratrol, and is activated by SIRT1 inhibitors, such as nicotinamide and splitomicin.[117] *SIRT1* knockdown reverses the inhibition of HIF-1α acetylation and activation by resveratrol, suggesting that resveratrol inhibits HIF-1α through SIRT1 activation.

3.3 | Effect of resveratrol on hypoxia

Resveratrol inhibits hypoxia-induced HIF-1α and VEGF expression in human cancer cells via multiple mechanisms, including interference with protein translational regulation and promotion of HIF-1α protein degradation.[121-123] In one such mechanism, inhibition of protein kinase B and mitogen-activated protein kinase phosphorylation by resveratrol plays a partial role in the downregulation of HIF-1α expression. An additional translation-level mechanism involves the

inhibition of protein translational regulators, including Mr 70,000 ribosomal protein S6 kinase 1, S6 ribosomal protein, eukaryotic initiation factor 4E-binding protein 1, and eukaryotic initiation factor 4E. Finally, resveratrol also induces substantial HIF-1α protein degradation via the proteasome pathway.[123]

Based on these findings, we examined the effects of resveratrol on HIF-1α and VEGF expression in KGN cells under $CoCl_2$-induced hypoxic conditions (Figure 1G–I).[92] HIF-1α protein levels significantly increase in response to hypoxia, an induction which is significantly suppressed by treatment with resveratrol in a dose-dependent manner. $CoCl_2$ rapidly induces HIF-1α protein accumulation due to a marked decrease in HIF-1α protein degradation, indicating that resveratrol may substantially induce HIF-1α protein degradation under hypoxic conditions. Resveratrol also attenuates $CoCl_2$-induced production of VEGF.

4 | MITOCHONDRIAL BIOGENESIS AND ITS RELATION TO HYPOXIA

4.1 | Mitochondrial biogenesis

Mitochondria are the most dynamically responsive detection systems in eukaryotic cells, satisfying metabolic energy demands, supplying biosynthetic precursors, and consequently regulating diverse processes including proliferation, immune response, apoptosis, and cell viability.[124-127] Cells can degrade damaged mitochondria via the process of mitophagy and, under appropriate conditions, stimulate functional mitochondria to proliferate through mitochondrial biogenesis, a complex process consisting of both the growth and the division of preexisting mitochondria.[128]

4.2 | Deacetylation of PGC-1 and mitochondrial biogenesis by SIRT1

Recent studies have demonstrated that SIRT1 promotes mitochondrial biogenesis by deacetylation of target proteins, such as PGC-1α, which suggests the potential therapeutic benefits of SIRT1 activation in metabolic and aging-related diseases.[129-131] Both SIRT1 and the nuclear transcription factor PGC-1α have been found in the mitochondria of human cell lines and platelets, as well as in various mouse organs.

Within the mitochondria, deacetylase and its substrate are associated with mtDNA nucleoids and mitochondrial transcription factor A (TFAM), a key mitochondrial gene transcription factor and mtDNA copy number regulator.[132,133] These findings suggest that SIRT1 and PGC-1α may also directly affect mitochondrial transcription (Figure 2).

TFAM and mitochondrial transcription factors B1 and B2 are critical in the regulation of replication, transcription, and maintenance during mitochondrial biogenesis.[130] SIRT1 is primarily located in the nucleus, but its activities greatly impact mitochondrial biogenesis and turnover.[36] Mitochondrial biogenesis involves

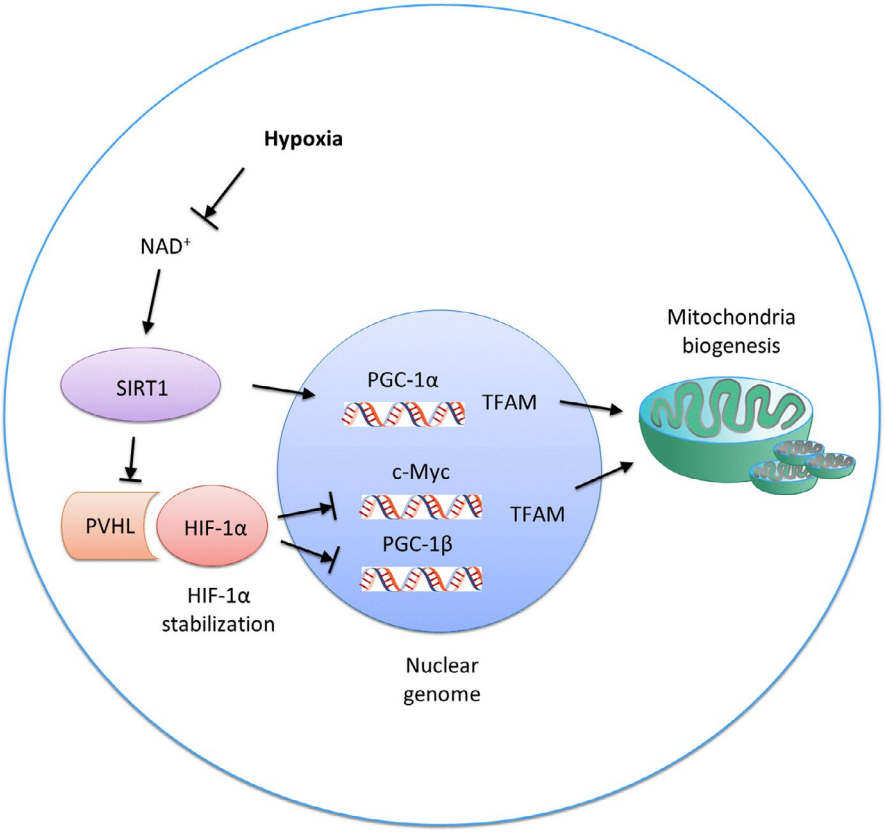

FIGURE 2 Regulation of mitochondria biogenesis by SIRT1 and HIF-1α during hypoxia. During hypoxia, the activity of SIRT1 in the nucleus is reduced, which decreases Von Hippel Lindau tumor suppressor levels and subsequently stabilizes HIF-1α. Activated HIF-1α reduces c-Myc activity and subsequently reduces transcription of mitochondrial transcription factor A. PGC-1β activity is also inhibited by HIF-1α, resulting in the downregulation of mitochondrial genes. SIRT1 reduction suppresses PGC-1α activity and prevents mitochondrial synthesis

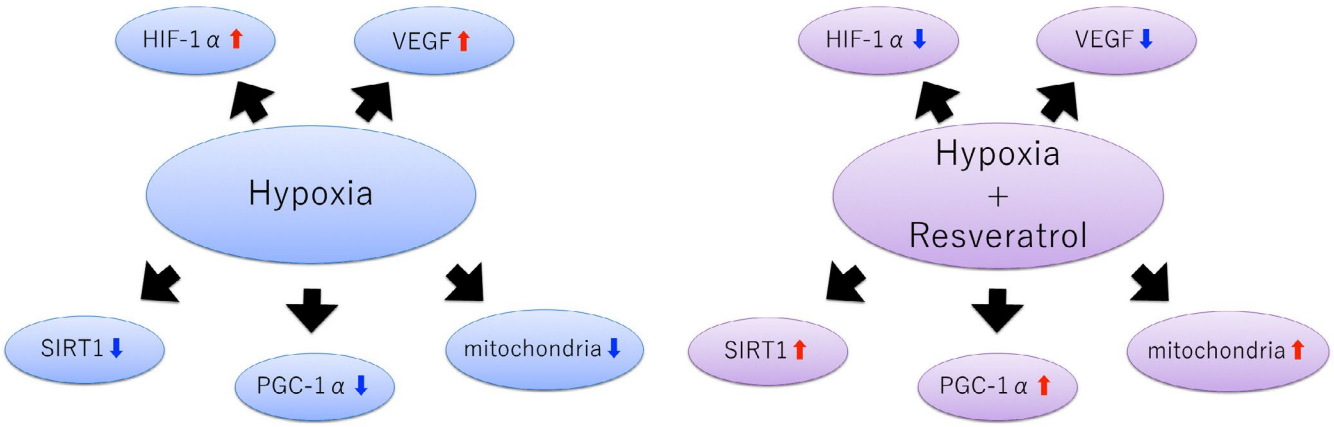

FIGURE 3 Effects of resveratrol on hypoxia. Resveratrol exerts protective effects against hypoxic stress

the transcription of both nuclear and mtDNA-encoded genes and is orchestrated by the PGC-1 family of transcriptional coactivators.[42,134] The PGC-1 family consists of three members: PGC-1α, PGC-1β, and the PGC-related coactivator.[135] PGC-1α, often cited as a master regulator of mitochondrial biogenesis, co-activates the transcription of nuclear respiratory factor 1 and 2, which, in turn, regulate TFAM transcription.[130,136,137] TFAM translocates to the mitochondrial matrix, where it stimulates mtDNA replication and mitochondrial gene expression. PGC-1α undergoes several modes of post-translational modifications, including acetylation and phosphorylation.

Acetylation alters the localization of PGC-1α in the nucleus and inhibits its transcriptional activity. Conversely, several studies have demonstrated that PGC-1α deacetylation is dependent on SIRT1 activity, which increases PGC-1α transcriptional activity.[138-140] Given the reliance of PGC-1α activity on its acetylation status, investigations on metabolic regulation and mitochondrial biogenesis have focused on the connection between SIRT1 and PGC-1α. Nemoto's group provided clear biochemical evidence that SIRT1 physically and functionally interacts with PGC-1α.[139]

4.3 | Hypoxia and mitochondrial biogenesis

During the aging process, HIF-1α suppresses mitochondrial biogenesis, impairing energy-dependent cellular processes, including cell and tissue repair.[32] HIF-1α involvement in mitochondrial biogenesis regulation and nuclear-mitochondrial communication modulation during aging is independent of PGC-1α.[43] The upregulation of HIF-1α activates the *Mxi1* gene, which encodes a c-Myc transcriptional repressor, resulting in an interruption of the c-Myc and TFAM binding, thus further suppressing TFAM promoter activity and mitochondrial biogenesis.[43]

PGC-1β, an additional master regulator of mitochondrial biogenesis, oxidative metabolism, and antioxidant defense, is preferentially expressed in high oxidative capacity tissue, where it participates in the metabolic response to high energy demand by regulating mitochondrial biogenesis.[141] HIF-1α also negatively regulates PGC-1β activity. In the cardiac ventricles of hypoxic mice, increased HIF-1α expression results in decreased PGC-1β mRNA and protein levels due to HIF-1α binding. Conversely, degradation of HIF-1α leads to PGC-1β release, which subsequently promotes mitochondrial biogenesis.[142]

During the hypoxia- or aging-induced decline in nuclear energy state or NAD^+ levels, the nuclear SIRT1 activity is reduced, downregulating the Von Hippel-Lindau protein and stabilizing the expression of HIF-1α. The latter subsequently reduces c-Myc activity and prevents TFAM transcription, which is required for replication, transcription, and maintenance of mitochondrial biogenesis. PGC-1β activity is also inhibited by its interaction with HIF-1α, resulting in the downregulation of mitochondrial genes[21,26] (Figure 2).

5 | CONCLUSION AND FUTURE PERSPECTIVE

Due to defects in the construction of vascular network surrounding the ovaries, maternal aging can cause ovarian hypoxia, which is assumed to affect the growth and development of ovarian follicles. Resveratrol enhances SIRT1 expression and mitochondrial function under hypoxic conditions, suggesting that it exerts a protective effect against hypoxia (Figure 3). Resveratrol may prevent mitochondrial dysfunction due to hypoxia or aging, and resveratrol treatment may be a potential therapy for treating infertility.

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CONFLICT OF INTEREST

All authors declare having no conflicts of interest.

HUMAN RIGHTS STATEMENT AND INFORMED CONCENT

This article does not contain any study with human participants that have been performed by any of the authors.

ANIMAL STUDIES

This article does not contain any study with animal participants that have been performed by any of the authors.

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