DERLEME REVIEW

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Effects of Sirtuins on Female Reproductivity and Oocyte Quality: Traditional Review

Sirtuinlerin Oosit Kalitesi ve Kadın Üremesi Üzerine Etkisi: Geleneksel Derleme

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ABSTRACT Sirtuins (SIRTs) are described as a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases and is able to catalyze post-translational modifications of proteins. It has been documented that, SIRTs respond to metabolic challenges, inflammation molecules, and oxidative stress. Many studies have linked SIRTs with longevity and having anti-aging activity. Our knowledge of SIRTs in reproduction has grown increasingly over the last few years. The majority of these research is carried out primarily on the effects on SIRT1 on female reproduction. It has been demonstarted that down-regulating SIRT1 trigers the reduction of ovarian reserve. Many research has demonstrated that, SIRT1 regulates proliferation and apoptosis in granulosa cells. Activity studies of SIRTs opened the discoveries of the functional aspects of different types of SIRTs in improving the overall quality of in vitro oocytes in humans and animal models. It has been documented that, SIRT1, SIRT2 and SIRT3 protect oocytes against postovulatory aging. The relationship between derangement of SIRT signaling and the imbalance of reactive oxygen species and antioxidant defenses in female reproductive organs has also been documented. The present review aims to put forward information on the mechanism and cellular role of SIRTs and give an update of sirtuin research in female reproduction under physiological and pathological conditions. The final goal of this work is to put forward the therapeutic potential of SIRTs in female infertility.

Keywords: Sirtuins; oocyte; ovary; reproduction; infertility

ÖZET Sirtuinler (SIRT), proteinlerin translasyon sonrası modifikasyonlarını katalize eden bir nikotinamid adenin dinükleotid (NAD+) bağımlı deasetilaz ailesidir. Metabolik zorluklara, inflamatuar sinyallere veya hipoksik/oksidatif strese yanıt verirler ve yaşlanma ve uzun yaşam ile ilişkilidirler. SIRT'ler ile ilgili üreme alanındaki bilgimiz son birkaç yılda giderek artmıştır. Şimdiye kadar yapılan çalışmaların çoğu kadın üremesine dönük olup, SIRT1'e odaklanılmıştır. SIRT1 sentezinin azalması sonucunda ovaryan rezervin de azaldığı kanıtlanmıştır. SIRT1'in, granüloza hücre proliferasyonu ve apoptozunu düzenlediği de gösterilmiştir. SIRT'lerin biyokimyasal aktivitesinin ortaya çıkarılmasıyla SIRT1, SIRT2, SIRT3 ve SIRT6'nın insan ve hayvan modellerinde in vitro olarak geliştirilen oositler üzerindeki rollerinin keşfedilmesine yol açmıştır. Son zamanlarda SIRT1, SIRT2 ve SIRT3 oositin postovulatuar yaşlanmaya karşı koruyucuları ortaya çıkmıştır. Ayrıca SIRT'lerin etkilediği sinyal yolaklarının düzensizleşmesi sonucu, kadın üreme organlarında reaktif oksijen türleri ve antioksidan savunma mekanizmalarındaki dengesizlik gösterilmiştir. Bu derleme, kadın üremesinde fizyolojik ve patolojik koşullar altında SIRT'lerin etki mekanizmaları ve hücresel rolü hakkında güncel bilgi aktarmayı amaçlamaktadır. Bu çalışmanın nihai amacı, kadın infertilitesinde tedavi amaçlı, SIRT'lerin potansiyel bir molekül olabileceği konusunu gündeme taşımaktır.

Anahtar Kelimeler: Sirtuinler; oosit; ovaryum; üreme; infertilite

SIRTs are described in the deacetylases class III family. The members which are induced by nicotinamide adenine dinucleotide (NAD^+) and are closely associated with various deoxyribonucleic acid (DNA) histone proteins. In humans, SIRTs family is composed of seven members; SIRT1-SIRT7. The majority of SIRTs show NAD^+-dependent deacetylase activity. SIRT4 and SIRT6 function as mono-adenosine triphosphate-ribosyl transferase. SIRT5 besides deacetylation, it can also generate demalonylation and desuccinylation. The presence of SIRTs has been reported to be present in various compartments in the cell for example; SIRT1, SIRT6, and SIRT7 was located in the nucleus, SIRT3, SIRT4, and SIRT5 in the mitochondria and SIRT2 in the cytosol. Recents investigations demonstrated active involvement of

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SIRTs in the modulation of many functional aspects of the ovaries. It has been demonstrated that, endocrine factors including SIRTs can influene the physiology of female reproductive system by stimulating the cellular elements of the ovaries.[1,2] It is documented that, SIRTs can affect cellular activities through down-regulating mammalian target of rapamycin (mTOR) and related intracellular signaling pathways.[3] Recent studies has examined SIRTs and their regulators extensively and have put forward their potential role in diagnosis and treatment in some disorders.

MECHANISMS OF ACTION OF THE SIRTUINS

Redox imbalance and decreased oxygen is a crucial environmental factor that is regulated by the cells. It is reported that, SIRT1 acts as a redox and oxygen sensor. In hypoxic environment, decreased NAD^+ concentrations suppresses the synthesis of SIRT1 levels.[4] A nutritional study in mice compared the effects on hepatic CREB-regulated transcription coactivator 2 (CRTC2) activity in short-term fasting (6-8 hours), or long-term fasting (18-24 hours) conditions.[5] In the same study the authors suggested that, during the initial fasting phase, gluconeogenesis is inhibited by the SIRT1.[5]

In muscle, SIRT1 synthesis was decreased in response to high lipid diet.[6]

The nuclear factor (NF) is well known for its major functions in the inflammatory reactions. It has been documented that, by the deacetylation mechanism, SIRT1 inhibits the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and therefore, decreases the concentration of reactive oxygen species (ROS) and inflammatory reactions.[7]

SIRT2 on the other hand, was demonstrated to be involved in regulating glucose and lipid metabolism via the activity of deacetylation. In addition, SIRT2 by stimulating phosphatidylinositol 3 kinase/protein kinase B (KB/Akt) pathway it regulates the activity of insulin. It is well known that, this pathway is involved in the activation of insulin receptor.[8] In a recent study, SIRT2 have been shown to increase the effect of pyruvate kinase (PK), phosphoenolpyruvate carboxylase, and phosphoglycerate mutase activity and therefore enhancing the tricarboxylic acid cycle.[9]

It has been suggested that, SIRT1 and SIRT2 is involved in the survival and functional aspects of neurons. Many research indicates that, SIRT1 and SIRT2 can be regarded as a novel target for the prevention of neurodegenerative diseases. Among the findings of these publications, it was demonstrated that, SIRT2 play a crucial role in neuorinflammation. In addition, in Parkinson's animal model it was demonstrated that, SIRT2 has a neuroprotective role and also induces neurogenesis in the hippocampus.[10-12]

SIRTS AND AGING

Aging is regarded as a physiological process linked to cellular senescence with declined metabolism.[13] It has been documented by many studies that, 5'AMP-activated protein kinase (AMPK) is involved in preventing aging and cellular senescence.[14,15] AMPK signaling has also been recognized to activate autophagy through suppression of the mTOR pathway.[16] There are various pharmacological inducers of AMPK and some are metformin and berberine. Many studies have put forward the positive effects of theses molecules in treating aged-related diseases such as metabolic, neurodegenerative, musculoskeletal and cancer.[17] It has been demonstrated that, autophgic mechanisms is abnormal and impaired in elderly and activity of autophagy is crucial for degrading nonfunctional or injured structural elements such as proteins and organells.[18] Increased amount of evidence showed that, the autophagic mechanisms decline with age.[19] In these studies the autophagy was investigated by assessment of p62 protein, lysosomal hydrolases and by visualizing the presence of green fluorescent protein-tagged microtubule-associated protein light chain 3 protein.[19] In addition to these findings, a decline of NAD^+ is also present in the aged individuals and the mechanisms for this decrease is not fully understood.[20] The same authors showed that, administration of NAD^+ precursors to the aged mice expressed remarkable improvement in the age-related features.[20] Furthermore, AMPK besides increa-

sing the levels of NAD^+ it also increses the levels of SIRT1 and this pathway is mediated by nicotinamide phosphoribosyltransferase, an enzyme which is crucial in the synthesis of NAD^+.[21,22]

Several studies has demonstrated that, SIRT1 has important activating effect in the growth of mesenchymal stem cells, and preventing replicative senescence by activating the transcription of human telomearse reverse transcriptase gene.[23,24] In addition, SIRT1 deletion shows a slow downregulation of cell growth and therefore, significantly increases the senescence time phase.[23] It was documented by Xu and co-workers that, SIRT1 induced the activity of miR-22, a molecule that is involved in the senescence mechanisms.[25] On the other hand, the production of SIRT1 can be regulated by micro ribonucleic acid (miRNA)-a molecule that suppresses the synthesis of messenger ribonucleic acid (mRNA) translation.[26] In addition, some studies have demonstrated a robust age dependent decrease in SIRT1 activity in the liver, heart, kidney, lung, muscles, and cerebellum of the rat.[27,28] Moreover, SIRT1 concentration and production was decreased in CD-1 aged mice.[29]

SIRTS AND REPRODUCTION

Reproduction, is one of the fundemental biological event that maintains the presence of the species. It is important to note that, the content of the primordial follicles and the quality of the oocytes is inversly effected by the aging process, hormonal changes and other external envoronmental factors which results in inferterlity. The ovarian cycle is regulated by many factors and hormonal mechanisms including SIRTs.[30] The increasing amount of findings suggests that, SIRTs may be engaged in controlling both the human and animal reproductive mechanisms and it may be regarded as a potential candidate to treat certain reproductive related deseases.

SIRTS IN THE OVARY

ROS is an important phenomenon that is involved in afffecting many cellular processes including folliculogenesis and oocyte development and maturation.[31] SIRTs is very well known to be the active molecule in aging and cellular metabolism and this effect is primarily achieved by its potential role in reducing the damage of oxidative damage.[32] It is known that aging process decreases the quality of the oocytes and reducing the effectivness of the oocyte mitochondria and enhancing the DNA breaks by oxidative damage. However, only recent studies have pointed out the importance of SIRTs in regulating the oocyte quality especially in the aged conditions.[32] In the oocytes, it was demonstrated that, SIRT6 is expressed in high levels and in the cumulus cells SIRT1, SIRT2, SIRT4, and SIRT6 were also expressed in high levels.[33] The same authors compared the levels of SIRTs between the young and old mice and found that there were significant decrease in SIRT2 and SIRT6 transcripts in cumulus cells of aged mice. The authors suggested the presence of a possible mechanism between the quality of the oocytes and aging processes via regulating the activity of cumulus cells through SIRTs. These findings may be important in aged related disorders and for candidates that may have potential clinical applications especially in aged women and one of the novel candidate may be the surtuins.[33]

Luo et al. examined the follicular fluid from patients of different diseases.[34] They demonstrated an overexpression of microRNA 23a (miR-23a) which inhibited SIRT1 expression and increased apoptosis in the granulosa cells. The association of SIRTs with the regulation of ovarian activity was described by Sirotkin.[1] The author suggested that, the reproductive functions such as proliferation and apoptosis is regulated by mTOR. Recent studies detected SIRT1 in the follicles, ovarian epithelium, stromal and granulosa cells and SIRT3 and SIRT5 was identified in granulosa cells and cumulus oophorus.[35,36]

Increased amount of studies have demonstrated SIRT3 as prime molecule in regulating the activity of the mitochondria through the acetylation of mitochondrial and scavenging proteins. Zhao et al. demonstrated the role of SIRT3 in the formation of new mitochondria and its role in the oocyte quality.[37] The same authors showed that, downregulation of the mitochondrial function leads to the accumulation of free radicals that promotes DNA and protein impairment and apoptosis.

Zhao and colleaques demonstrated a decrease in the levels of SIRT3, biogenesis and the number of mitochondria in human oocytes.[37] The same authors proposed that, human in vitro maturation (IVM)-metaphase II (MII) oocytes is influenced by decreased mitochondrial biosynthesis and insufficiency of SIRT3 mRNA.[37] Many results indicate that, there are potential factors including the SIRTs that are involved in the maturation of oocyte and SIRTs may be regarded as central target to improve IVM-MII oocyte quality. Furthermore, the results of these observations may highlight the clinical applications and the potential targets of future IVM procedures. Measuring sirtuin levels in the fluids can be regarded as a diagnostic tool to treat many ovarian disorders (Figure 1). It has been indicated that, SIRT1, SIRT3, SIRT5, and SIRT6 can be used as markers to describe normal and abnormal follicular development.

SIRTS AND OOCYTE

In the last decade there is an increasing expectations for assisted reproductive technology. Assisted reproductive technology, besides been high costly the outcome is also unpredictable and the higher the age of the patients gives more lesser chance to be successful. Generally speaking, as age increases embryo quality decreases due to the decrease in mitochondrial number in the oocytes with low adenosine triphosphate content and increase in the DNA variation and aneuploidy. Presently, anti-Mullerian hormone and antral follicle count in the serum are used to identify and detect the premature ovarian inadequacy.[38-41]

However, in recent years there are growing number evidence that show the involvement SIRTs in modulating and influencing many distinct ovarian functions such as; cell proliferation, apoptosis, folliculogenesis, oogenesis, and over all embryo development. Therefore, SIRTs may be used as a tool to identify premature ovarian failure.[42]

In parallel to this, it was shown that, in SIRT1-deficient mice model, plasma gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH) and follicle stimulating hormone was decreased. In addition, in the rat ovaries, increased SIRT1 synthesis via resveratrol, was correlated with the high concentration of LH receptors and enzymes.[43] These findings suggests that, SIRT1 may be regareded as an important factor that can promote and influence specific functional activities in the ovaries either direct effect or an indirect effect through GnRH. In the transfection studies, *SIRT1* gene construct induced proliferation and production of insulin like growth factor-1, testosterone and progesterone in porcine granulosa cells and mouse and human oocytes in culture.[37,44,45] Over all

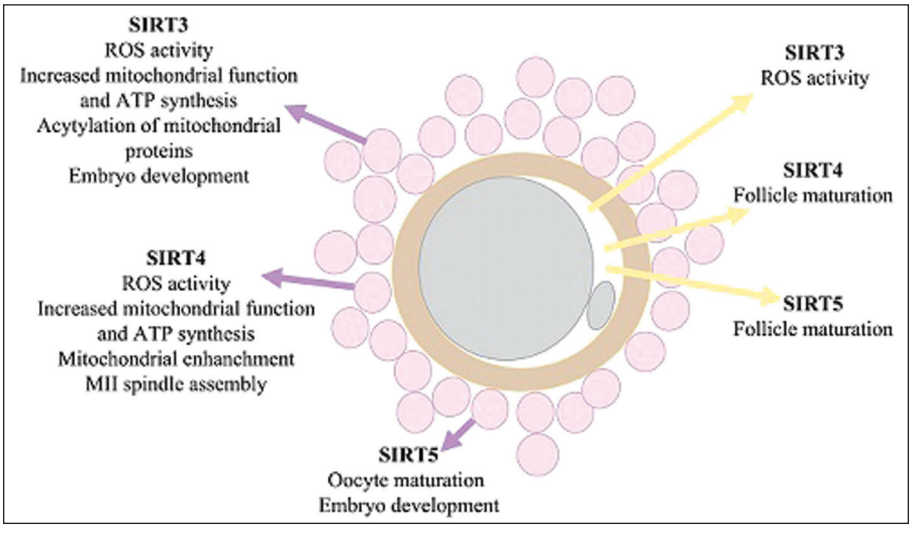

FIGURE 1: Mechanisms of action of sirtuins on oocytes and granulosa cells.
SIRT: Sirtuins; ROS: Reactive oxygen species; ATP: Adenosine triphosphate; MII: Metaphase II.

the these observations suggests that, SIRT1 can modulate and affect the activities of hormons that has active role in ovarian functions.[46] In addition, SIRTs can regulate follicular cell functions through inducing a distinct set of transcription factors such as; p53, NFkB, forkhead box L2, neurogenic locus notch homolog protein 3, signal transducer and activator of transcription 3 (Figure 2).[47,48] It has been demonstrated that, these molecules are effective in ovarian proliferation, apoptosis, and steroidogenesis.[37,44,46,49,50] A striking evidence was demonstrated in a mice that was deficient of SIRT1. It was reported that, these mice were infertile and along with other findings it was suggested by the authors that, SIRT1 can be regarded as a potential molecule for the regulation of ovarian functions.[42]

SIRTs can influnce the activity of the target cells directly by either increasing or decreasing the levels of certain molecules, but also it can affect the target cells indirectly by influencing the synthesis of a

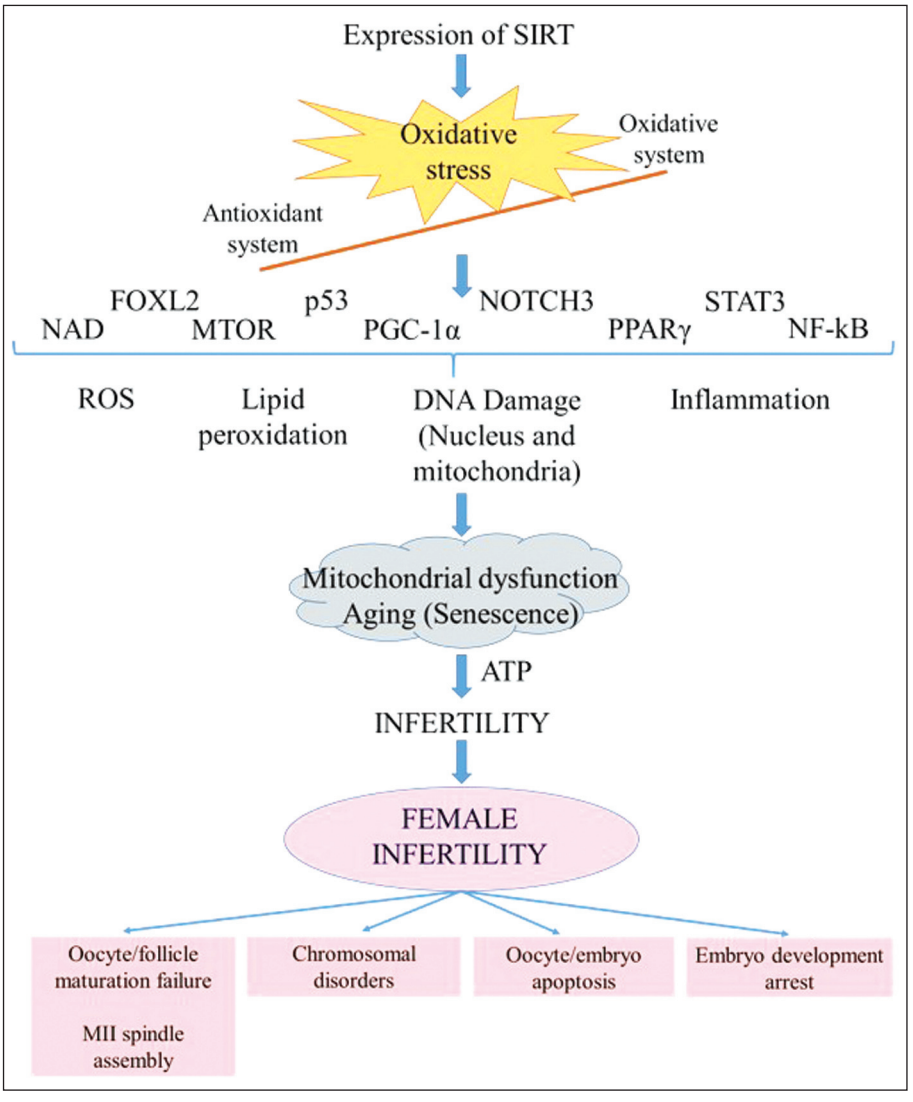

FIGURE 2: Effects of changes in SIRT expression on oocyte quality and female infertility.
SIRT: Sirtuins; FOXL2: Forkhead box L2; NAD: Nicotinamide adenine dinucleotide; mTOR: Mammalian target of rapamycin; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; NOTCH3: Notch homolog protein 3; PPARγ: Peroxisome proliferator-activated receptor gamma; STAT3: Transducer and activator of transcription 3; NF-KB: Nuclear factor kappa B; ROS: Reactive oxygen species; DNA: Deoxyribonucleic acid; ATP: Adenosine triphosphate; MII: Metaphase II.
Note that, changes in SIRTs expression, causes mitochondrial dysfunction and aging by increasing reactive oxygen species (ROS), lipid peroxidation, DNA damage and inflammation in oocytes and embryos which leads to female infertility.

synthetic or natural (plant-derived) molecule called mTOR. Many studies demonstrated the actions of mTOR inhibitors on various ovarian functions. It is known that, mTOR pathway is essential in proliferation, apoptosis, secretory activity, follicular development, and cancer formation of the ovaries. mTOR and SIRTs are functionally closely related. It was demonstrated that, resveratrol is an active mTOR blocker and mTOR is an inhibitor of SIRTs 1, 3, 4, and 7.[51-55] A pharmacological inhibitor of mTOR improved murine follicular cells and increased the lifespan of normal reproductive functions of the ovaries in rats.[42] It was demonstrated that, mTOR blockers induced SIRT1 and SIRT6 in ovarian cells.[43,51]

On the other hand, resveratrol which is known to turn on the synthetic pathway of the SIRTs, promoted ovarian follicular reserve and stopped the age-related outcomes such as infertility and other diseases in mice.[53,56] Another important study suggested that, the simplest way to enhance the synthesis of SIRTs is simply by caloric restriction. In another study, by restricting the caloric intake enhanced the production of SIRT1 in murine ovaries.[57]

Ovarian aging as mentioned earlier is an important phenomenon that is crucial in follicular development and oocyte quality. These changes may be the result of decrease in the levels of SIRT1, SIRT3, and SIRT6 in aged mice ovaries and decrease in the levels of SIRT3 and SIRT5 in aged women ovaries.[58]

It is evident that, in vitro fertilization and embryo transfer treatment is a process that allows the formation of oxidative stress of the oocytes and therefore, destructs the quality of the oocytes. Studies has demonstrated that, SIRT1 and AMPK pathway can be activated by metformin and resveratrol by activating the antioxidant systems in the polycystic ovary syndrome patients.[59] Therefore, SIRT1 has been suggested by many authors as a valuable endometrial marker in women with endometriosis.[60,61]

CONCLUSION

SIRTs besides being discovered in many organs in the body it is also present in the ovarian follicles, ovarian epithelium, ovarian stroma, granulosa cells and cumulus cells surrounding the oocyte. The level of surtins has been regarded to be an important marker in ovarian cells and has been associated with normal reproductive health. Taken together, observations on SIRTs has led to the idea that, SIRTs may be regarded as a potential molecule to detect the ovarian reserve and aged related damage of the normal ovarian tissue and in ovarian dysfunctions.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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REFERENCES

1. Sirotkin AV. The role and application of sirtuins and mtor signaling in the control of ovarian functions. Cells. 2016;5(4):42. [Crossref] [PubMed] [PMC]
2. Artimani T, Karimi J, Mehdizadeh M, Yavangi M, Khanlarzadeh E, Ghorbani M, et al. Evaluation of pro-oxidant-antioxidant balance (PAB) and its association with inflammatory cytokines in polycystic ovary syndrome (PCOS). Gynecol Endocrinol. 2018;34(2):148-52. [Crossref] [PubMed]
3. Yuan B, Schafferer S, Tang Q, Scheffler M, Nees J, Heil J, et al. A plasma metabolite panel as biomarkers for early primary breast cancer detection. Int J Cancer. 2019;144(11):2833-42. [Crossref] [PubMed]
4. Lim JH, Lee YM, Chun YS, Chen J, Kim JE, Park JW. Sirtuin 1 modulates cellular responses to hypoxia by deacetylating hypoxia-inducible factor 1alpha. Mol Cell. 2010;38(6):864-78. [Crossref] [PubMed]
5. Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, et al. A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. Nature. 2008;456(7219):269-73. [Crossref] [PubMed] [PMC]
6. Gerhart-Hines Z, Rodgers JT, Bare O, Lerin C, Kim SH, Mostoslavsky R, et al. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. EMBO J. 2007;26(7):1913-23. [Crossref] [PubMed] [PMC]
7. Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF-κB and SIRT1 in the regulation of inflammation and metabolic disorders. Cell Signal. 2013;25(10):1939-48. [Crossref] [PubMed]
8. Schultze SM, Hemmings BA, Niessen M, Tschopp O. PI3K/AKT, MAPK and AMPK signalling: protein kinases in glucose homeostasis. Expert Rev Mol Med. 2012;14:e1. [Crossref] [PubMed]
9. Wang T, Geng SL, Guan YM, Xu WH. Deacetylation of metabolic enzymes by Sirt2 modulates pyruvate homeostasis to extend insect lifespan. Aging (Albany NY). 2018;10(5):1053-72. [Crossref] [PubMed] [PMC]
10. Wang B, Zhang Y, Cao W, Wei X, Chen J, Ying W. SIRT2 Plays Significant Roles in Lipopolysaccharides-Induced Neuroinflammation and Brain Injury in Mice. Neurochem Res. 2016;41(9):2490-500. [Crossref] [PubMed]
11. Chen X, Wales P, Quinti L, Zuo F, Moniot S, Herisson F, et al. The sirtuin-2 inhibitor AK7 is neuroprotective in models of Parkinson's disease but not amyotrophic lateral sclerosis and cerebral ischemia. PLoS One. 2015;10(1):e0116919. [Crossref] [PubMed] [PMC]
12. Liu R, Dang W, Du Y, Zhou Q, Jiao K, Liu Z. SIRT2 is involved in the modulation of depressive behaviors. Sci Rep. 2015;5:8415. [Crossref] [PubMed] [PMC]
13. Toussaint O, Medrano EE, von Zglinicki T. Cellular and molecular mechanisms of stress-induced premature senescence (SIPS) of human diploid fibroblasts and melanocytes. Exp Gerontol. 2000;35(8):927-45. [Crossref] [PubMed]
14. Stenesen D, Suh JM, Seo J, Yu K, Lee KS, Kim JS, et al. Adenosine nucleotide biosynthesis and AMPK regulate adult life span and mediate the longevity benefit of caloric restriction in flies. Cell Metab. 2013;17(1):101-12. [Crossref] [PubMed] [PMC]
15. Ido Y, Duranton A, Lan F, Weikel KA, Breton L, Ruderman NB. Resveratrol prevents oxidative stress-induced senescence and proliferative dysfunction by activating the AMPK-FOXO3 cascade in cultured primary human keratinocytes. PLoS One. 2015;10(2):e0115341. [Crossref] [PubMed] [PMC]
16. Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. Ageing Res Rev. 2012;11(2):230-41. [Crossref] [PubMed]
17. Mo C, Wang L, Zhang J, Numazawa S, Tang H, Tang X, et al. The crosstalk between Nrf2 and AMPK signal pathways is important for the anti-inflammatory effect of berberine in LPS-stimulated macrophages and endotoxin-shocked mice. Antioxid Redox Signal. 2014;20(4):574-88. [Crossref] [PubMed] [PMC]
18. Lipinski MM, Zheng B, Lu T, Yan Z, Py BF, Ng A, et al. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. Proc Natl Acad Sci U S A. 2010;107(32):14164-9. [Crossref] [PubMed] [PMC]
19. Klionsky DJ, Abdalla FC, Abeliovich H, Abraham RT, Acevedo-Arozena A, Adeli K, et al. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy. 2012;8(4):445-44. [PubMed] [PMC]
20. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. 2013;155(7):1624-38. [Crossref] [PubMed] [PMC]
21. Han X, Tai H, Wang X, Wang Z, Zhou J, Wei X, et al. AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD(+) elevation. Aging Cell. 2016;15(3):416-27. [Crossref] [PubMed] [PMC]
22. Lee D, Goldberg AL. SIRT1 protein, by blocking the activities of transcription factors FoxO1 and FoxO3, inhibits muscle atrophy and promotes muscle growth. J Biol Chem. 2013;288(42):30515-26. [Crossref] [PubMed] [PMC]
23. Yuan HF, Zhai C, Yan XL, Zhao DD, Wang JX, Zeng Q, et al. SIRT1 is required for long-term growth of human mesenchymal stem cells. J Mol Med (Berl). 2012;90(4):389-400. [Crossref] [PubMed]
24. Yamashita S, Ogawa K, Ikei T, Udono M, Fujiki T, Katakura Y. SIRT1 prevents replicative senescence of normal human umbilical cord fibroblast through potentiating the transcription of human telomerase reverse transcriptase gene. Biochem Biophys Res Commun. 2012;417(1):630-4. [Crossref] [PubMed]
25. Xu D, Takeshita F, Hino Y, Fukunaga S, Kudo Y, Tamaki A, et al. miR-22 represses cancer progression by inducing cellular senescence. J Cell Biol. 2011;193(2):409-24. [Crossref] [PubMed] [PMC]
26. Revollo JR, Li X. The ways and means that fine tune Sirt1 activity. Trends Biochem Sci. 2013;38(3):160-7. [Crossref] [PubMed] [PMC]
27. Braidy N, Guillemin GJ, Mansour H, Chan-Ling T, Poljak A, Grant R. Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats. PLoS One. 2011;6(4):e19194. [Crossref] [PubMed] [PMC]
28. Falone S, D'Alessandro A, Mirabilio A, Cacchio M, Di Ilio C, Di Loreto S, et al. Late-onset running biphasically improves redox balance, energy- and methylglyoxal-related status, as well as SIRT1 expression in mouse hippocampus. PLoS One. 2012;7(10):e48334. [Crossref] [PubMed] [PMC]
29. Pallàs M, Pizarro JG, Gutierrez-Cuesta J, Crespo-Biel N, Alvira D, Tajes M, et al. Modulation of SIRT1 expression in different neurodegenerative models and human pathologies. Neuroscience. 2008;154(4):1388-97. [Crossref] [PubMed]
30. Roupa Z, Polikandrioti M, Sotiropoulou P, Faros E, Koulouri A, Wozniak G, et al. Causes of infertility in women at reproductive age. Heal Sci J. 2009;3(2):80-7. [Link]
31. Nu-ez-Calonge R, Cortés S, Gutierrez Gonzalez LM, Kireev R, Vara E, Ortega L, et al. Oxidative stress in follicular fluid of young women with low response compared with fertile oocyte donors. Reprod Biomed Online. 2016;32(4):446-56. [Crossref] [PubMed]

32. Marcu R, Wiczer BM, Neeley CK, Hawkins BJ. Mitochondrial matrix Ca^{2+} accumulation regulates cytosolic NAD^{+}/NADH metabolism, protein acetylation, and sirtuin expression. Mol Cell Biol. 2014;34(15):2890-902. [Crossref] [PubMed] [PMC]
33. Okamoto N, Kawamura K, Kawamura N, Nishijima C, Ishizuka B, Suzuki N, et al. Effects of maternal aging on expression of sirtuin genes in ovulated oocyte and cumulus cells. J Mamm Ova Res. 2013;30(1):24-9. [Crossref]
34. Luo H, Han Y, Liu J, Zhang Y. Identification of microRNAs in granulosa cells from patients with different levels of ovarian reserve function and the potential regulatory function of miR-23a in granulosa cell apoptosis. Gene. 2019;686:250-60. [Crossref] [PubMed]
35. Pacella-Ince L, Zander-Fox DL, Lan M. Mitochondrial SIRT3 and its target glutamate dehydrogenase are altered in follicular cells of women with reduced ovarian reserve or advanced maternal age. Hum Reprod. 2014;29(7):1490-9. [Crossref] [PubMed]
36. Pacella-Ince L, Zander-Fox DL, Lane M. Mitochondrial SIRT5 is present in follicular cells and is altered by reduced ovarian reserve and advanced maternal age. Reprod Fertil Dev. 2014;26(8):1072-83. [Crossref] [PubMed]
37. Zhao HC, Ding T, Ren Y, Li TJ, Li R, Fan Y, et al. Role of Sirt3 in mitochondrial biogenesis and developmental competence of human in vitro matured oocytes. Hum Reprod. 2016;31(3):607-22. [Crossref] [PubMed]
38. Izhar R, Husain S, Tahir S, Husain S. Occult form of premature ovarian insufficiency in women with infertility and oligomenorrhea as assessed by poor ovarian response criteria. J Reprod Infertil. 2017;18(4):361-7. [PubMed] [PMC]
39. Durlinger AL, Kramer P, Karels B, de Jong FH, Uilenbroek JT, Grootegoed JA, et al. Control of primordial follicle recruitment by anti-Müllerian hormone in the mouse ovary. Endocrinology. 1999;140(12):5789-96. [Crossref] [PubMed]
40. Pellatt L, Rice S, Dilaver N, Heshri A, Galea R, Brincat M, et al. Anti-Müllerian hormone reduces follicle sensitivity to follicle-stimulating hormone in human granulosa cells. Fertil Steril. 2011;96(5):1246-51.e1. [Crossref] [PubMed]
41. Grisendi V, La Marca A. Individualization of controlled ovarian stimulation in vitro fertilization using ovarian reserve markers. Minerva Ginecol. 2017;69(3):250-8. [Crossref] [PubMed]
42. Tatone C, Di Emidio G, Vitti M, Di Carlo M, Santini S Jr, D'Alessandro AM, et al. Sirtuin functions in female fertility: possible role in oxidative stress and aging. Oxid Med Cell Longev. 2015;2015:659687. [Crossref] [PubMed] [PMC]
43. Morita Y, Wada-Hiraike O, Yano T, Shirane A, Hirano M, Hiraike H, et al. Resveratrol promotes expression of SIRT1 and StAR in rat ovarian granulosa cells: an implicative role of SIRT1 in the ovary. Reprod Biol Endocrinol. 2012;10:14. [Crossref] [PubMed] [PMC]
44. Pavlová S, Klucska K, Vašíček D, Ryban L, Harrath AH, Alwasel SH, et al. The involvement of SIRT1 and transcription factor NF-κB (p50/p65) in regulation of porcine ovarian cell function. Anim Reprod Sci. 2013;140(3-4):180-8. [Crossref] [PubMed]
45. Sirotkin AV, Dekanová P, Harrath AH, Alwasel SH, Vašíček D. Interrelationships between sirtuin 1 and transcription factors p53 and NF-κB (p50/p65) in the control of ovarian cell apoptosis and proliferation. Cell Tissue Res. 2014;358(2):627-32. [Crossref] [PubMed]
46. Sirotkin AV, Alexa R, Dekanová P, Kádasi A, Štochmaľová A, Grossmann R, et al. The mTOR system can affect basic porcine ovarian cell functions and mediate the effect of ovarian hormonal regulators. Int J Pharmacol. 2015;11(6):570-8. [Crossref]
47. Alam F, Syed H, Amjad S, Baig M, Khan TA, Rehman R. Interplay between oxidative stress, SIRT1, reproductive and metabolic functions. Curr Res Physiol. 2021;4:119-124. [Crossref] [PubMed] [PMC]
48. Barbagallo F, Condorelli RA, Mongioì LM, Cannarella R, Cimino L, Magagnini MC, et al. Molecular Mechanisms Underlying the Relationship between Obesity and Male Infertility. Metabolites. 2021;11(12):840. [Crossref] [PubMed] [PMC]
49. Benayoun BA, Georges AB, L'Hôte D, Andersson N, Dipietromaria A, Todeschini AL, et al. Transcription factor FOXL2 protects granulosa cells from stress and delays cell cycle: role of its regulation by the SIRT1 deacetylase. Hum Mol Genet. 2011;20(9):1673-86. [Crossref] [PubMed]
50. Zhang J, Yin XJ, Xu CJ, Ning YX, Chen M, Zhang H, et al. The histone deacetylase SIRT6 inhibits ovarian cancer cell proliferation via down-regulation of Notch 3 expression. Eur Rev Med Pharmacol Sci. 2015;19(5):818-24. [PubMed]
51. Zhang XM, Li L, Xu JJ, Wang N, Liu WJ, Lin XH, et al. Rapamycin preserves the follicle pool reserve and prolongs the ovarian lifespan of female rats via modulating mTOR activation and sirtuin expression. Gene. 2013;523(1):82-7. [Crossref] [PubMed]
52. Kashiyama T, Oda K, Ikeda Y, Shiose Y, Hirota Y, Inaba K, et al. Antitumor activity and induction of TP53-dependent apoptosis toward ovarian clear cell adenocarcinoma by the dual PI3K/mTOR inhibitor DS-7423. PLoS One. 2014;9(2):e87220. [Crossref] [PubMed] [PMC]
53. Liu M, Yin Y, Ye X, Zeng M, Zhao Q, Keefe DL, et al. Resveratrol protects against age-associated infertility in mice. Hum Reprod. 2013;28(3):707-17. [Crossref] [PubMed]
54. Zhou XL, Xu JJ, Ni YH, Chen XC, Zhang HX, Zhang XM, et al. SIRT1 activator (SRT1720) improves the follicle reserve and prolongs the ovarian lifespan of diet-induced obesity in female mice via activating SIRT1 and suppressing mTOR signaling. J Ovarian Res. 2014;7:97. [Crossref] [PubMed] [PMC]
55. Yu J, Yaba A, Kasiman C, Thomson T, Johnson J. mTOR controls ovarian follicle growth by regulating granulosa cell proliferation. PLoS One. 2011;6(7):e21415. [Crossref] [PubMed] [PMC]
56. Ortega I, Villanueva JA, Wong DH, Cress AB, Sokalska A, Stanley SD, et al. Resveratrol reduces steroidogenesis in rat ovarian theca-interstitial cells: the role of inhibition of Akt/PKB signaling pathway. Endocrinology. 2012;153(8):4019-29. [Crossref] [PubMed] [PMC]
57. Liu WJ, Zhang XM, Wang N, Zhou XL, Fu YC, Luo LL. Calorie restriction inhibits ovarian follicle development and follicle loss through activating SIRT1 signaling in mice. Eur J Med Res. 2015;20(1):22. [Crossref] [PubMed] [PMC]
58. Zhang J, Fang L, Lu Z, Xiong J, Wu M, Shi L, et al. Are sirtuins markers of ovarian aging? Gene. 2016;575(2 Pt 3):680-6. [Crossref] [PubMed]
59. Furat Rencber S, Kurnaz Ozbek S, Eraldemır C, Sezer Z, Kum T, Ceylan S, et al. Effect of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS: an experimental study. J Ovarian Res. 2018;11(1):55. [Crossref] [PubMed] [PMC]
60. Yoo JY, Kim TH, Fazleabas AT, Palomino WA, Ahn SH, Tayade C, et al. KRAS Activation and over-expression of SIRT1/BCL6 contributes to the pathogenesis of endometriosis and progesterone resistance. Sci Rep. 2017;7(1):6765. [Crossref] [PubMed] [PMC]
61. Yao LN, Zhang TF, Lin WQ, Jiang N, Cao HF, Li H, et al. Value of serum and follicular fluid sirtuin (SIRT)1 and SIRT2 protein levels in predicting the outcome of assisted reproduction. Ann Transl Med. 2021;9(4):343. [Crossref] [PubMed] [PMC]