



Sirtuins and their role in ovarian aging-related fibrosis predisposing to ovarian cancer



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The pursuit of understanding early genetic or protein markers for ovarian aging has garnered considerable attention in the realm of reproductive medicine. Sirtuins (SIRT) are a group of proteins that are NAD⁺-dependent, and thanks to their properties, they are able to change the acetylation profile of proteins and post-translationally modify their functions, too. Previous research provided evidence that SIRT influence fibrosis levels in several organs. With regard to ovaries, fibrosis is one of the features of aged ovaries and also creates a metastasis-friendly environment, thus can also be a seedbed for the development of primary cancerous lesions. Ovarian cancer remains a formidable challenge in oncology due to its high prevalence, insidious onset, and frequent recurrence. Noteworthy, ovarian cancer is the seventh most common cancer among women and the eighth leading cause of cancer death worldwide. Ovarian fibrosis runs concurrently with the activation of TGF- β /Smads signaling, as well as inflammasome (NLRP3), nuclear factor κ B (NF κ B) and forkhead box O (FOXO) attenuation. Reduced levels of certain sirtuins resulting from decreased nicotinamide adenine dinucleotide (NAD⁺) may underlie the dysregulation of the aforementioned signaling pathways and therefore represent a potential therapeutic target. This review elucidates the role of SIRT in ovarian aging-related fibrosis as a process that predisposes to tumorigenesis.

In the quest to comprehend the complexities of the aging phenomenon in the female reproductive system, early markers for ovarian aging, fibrosis, and cancer offer critical insights into the intricate cellular pathways that deteriorate as women's ovaries age, presenting substantial implications for fertility treatments and reproductive health strategies (Fig. 1). Among various regulators of cellular homeostasis, the sirtuin (SIRT) family—comprising seven NAD⁺-dependent enzymes, SIRT1–SIRT7—acts as crucial sensors of energy and redox status¹.

SIRT are a family of seven enzymes: SIRT1–7, that play a key role in regulating protein function through post-translational modifications, primarily by removing acetyl groups². Their roles in controlling oxidative stress, genomic stability, and cell fate position them as central modulators of both ovarian fibrosis and tumorigenesis. SIRT1 is widely recognized for its antifibrotic and tumor-suppressive effects through regulation of TGF- β , p53, and NF- κ B pathways, although in certain cancers, its overexpression may support tumor progression^{3–6}. SIRT2 regulates cell

division and spindle integrity and has been shown to impact fibrotic signalling via DKK1 and Smad3, while also displaying tumor-suppressive properties in ovarian cancer^{7–9}. SIRT3, the principal mitochondrial deacetylase, protects against oxidative stress and supports mitochondrial function; its decline with age promotes fibrosis and is associated with poor ovarian cancer prognosis^{10,11}. SIRT4, though less well characterized, influences oocyte maturation and may contribute to mitotic stability; its aberrant expression is linked to both ovarian aging and malignancy^{12–14}. SIRT5, through its desuccinylase activity, modulates metabolic enzymes involved in redox balance; it may promote chemoresistance in ovarian tumors and has been found altered in fibrotic ovarian conditions^{15–17}. Nuclear sirtuins SIRT6 and SIRT7 are vital for chromatin remodeling and DNA repair; SIRT6 has been shown to counteract fibrotic matrix deposition and oxidative stress, while SIRT7 supports oocyte quality and genome maintenance, both showing deregulation in ovarian aging and cancer^{18–22}.

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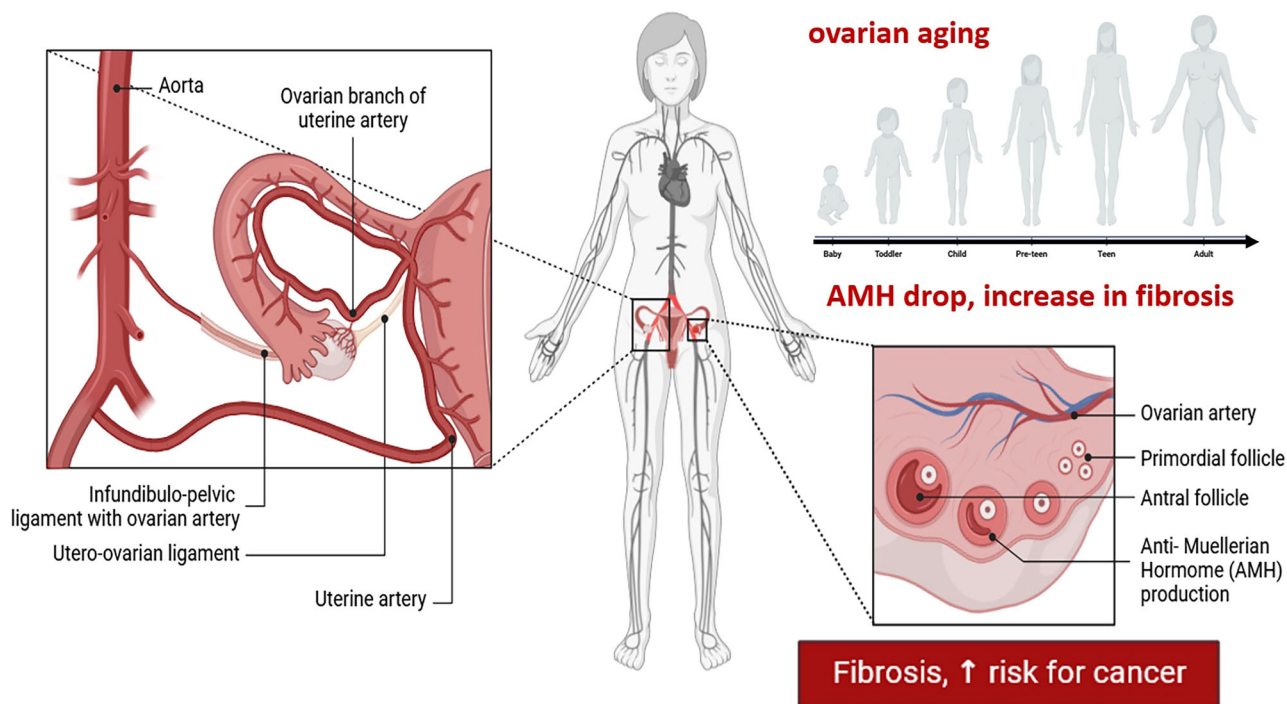


Fig. 1 | Scheme showing the phenomenon of ovarian aging and its effects on the decrease of the antral follicle count (AFC), and of the anti-Muellerian Hormone (AMH) in the bloodstream of women with advancing age. With increasing age, symptoms of fibrosis increase, and by this, the risk for tumorigenesis is elevated, too.

As NAD⁺ levels decline with age, the activity of all SIRT's diminishes, contributing to dysregulation of cellular stress responses, extracellular matrix remodeling, and ultimately creating a microenvironment that favors both fibrosis and tumor development^{23–26}. Age-related ovarian dysfunction has been linked to decreased levels of SIRT's²⁷, i.e., decreased ovarian reserve, which has been associated with decreased levels of SIRT1, SIRT3 and SIRT6²⁶. Another feature of aging is ovarian fibrosis²⁸, and, as mentioned earlier, fibrosis can promote conditions similar to the pre-metastatic niche²⁹. Tumor-associated fibrosis may have a variety of functions, including a role in drug resistance. Indeed, targeting Transforming growth factor- β (TGF- β), which leads to inhibition of fibrosis, can sensitize the tumor to immunotherapies^{30,31}. However, some studies claim that ovarian fibrosis may contribute to the development of a microenvironment favourable for tumor growth by mobilizing ECM components, primarily collagen, and activating fibrotic pathways, e.g. TGF- β , which are closely related to the potential of cells to undergo the EMT process. Interestingly, most malignant tumors are accompanied by severe stromal changes³², and increasing stiffness of ovarian tissue facilitates tumor invasion or metastasis³³. Fibrotic ovaries are also encountered in postmenopausal and advanced-age women, a period of life that predisposes to the development of ovarian cancer (OC)³⁴. The age-related accumulation of damage caused by increasing oxido-inflammatory stress contributes to worsening changes in the ovarian stroma and capsule, which may be linked to a higher predisposition to OC²⁹.

This review aims to explore the multifaceted roles of sirtuins in ovarian aging-related fibrosis and their contribution to ovarian cancer predisposition, integrating their molecular actions within key signaling pathways and physiological contexts.

Sirtuins and TGF- β and ECM modifications in ovarian fibrosis

Transforming growth factor- β (TGF- β) is a major signaling pathway responsible for the activation of fibroblasts, involved in fibrosis in many organs, including the heart, lung, liver, and ovaries³⁵. In recent years, research has significantly focused on ovarian fibrosis as a feature of aging^{36,37} and the associated predisposition to tumorigenesis³⁸. TGF- β also controls

the pathways responsible for epithelial-to-mesenchymal transition (EMT) (Fig. 2), endothelial-to-mesenchymal transition (EndMT), and Wnt/ β -Catenin - key fibrosis pathways during carcinogenesis^{39,40}. Given that the acetylation level of Small Mother Against Decapentaplegic (Smads) transcription factors is crucial for the events triggered by TGF- β receptor 2 (TGFR2) and TGFR1 activation, sirtuins, as constitutive deacetylases, may play a key role in regulating the activation of Smad2, Smad3, Smad4 and Smad7 and translocation of the Smad2/3 complex to the nucleus⁴¹. Interestingly, the dynamics of sirtuin activity may differ from one ovarian cell to another, as with age, the SIRT's activity is attenuated in granulosa cells and increased in oocytes, suggesting a different role for each cell in aging processes and a possible influence on fibrosis progression⁴² [Table 1]. Smads deficiency or dysfunction can have consequences on granulosa cell function as well as on thecal cells, causing fertility defects⁴³. Interestingly, the thecal cells, which are the first ovarian cells to up-regulate fibrosis triggered by the TGF β 1, TGF β 2, and Smad3 as a result of aging, may play a key role in fibroblast activation⁴². TGF- β target genes involved in ovarian fibrosis include alpha-smooth muscle actin (α -SMA) and Col1a1, Col1a2, and Col3a1. While the first is a marker of myofibroblasts and activated fibroblasts, the latter are the main genes responsible for remodelling the ECM into excessive collagen and thickening its fibres. The expression of those genes increases with age, and they have a role also in the pathogenesis of other ovarian diseases, such as PCOS. Several populations of fibroblasts at different levels of differentiation and myofibroblasts with high α -SMA expression have been demonstrated in aging mice⁴⁴. Even though a differentiated pool of fibroblasts represents a physiological condition of a dynamic cycle enabling dependent on TGF- β signaling, the old mice showed an increased proportion of fibroblasts with a senescence-associated secretory phenotype (SASP)⁴⁴. Increased ovarian collagen deposition correlates with a decrease in SIRT1 expression in ovaries with PCOS^{45,46}, with a decrease in nicotinamide adenine dinucleotide (NAD⁺) levels with age in ovaries^{47,48}, and with a decrease in SIRT1 expression and reduced ovarian reserve⁴⁹. One of the few studies investigating the direct relationship of SIRT1 with Smads in ovaries shows that resveratrol downregulates Smad2/3 phosphorylation and inhibits follicle-stimulating hormone (FSH β) expression, but inhibition of SIRT1 did not affect the efficacy of resveratrol⁵⁰,

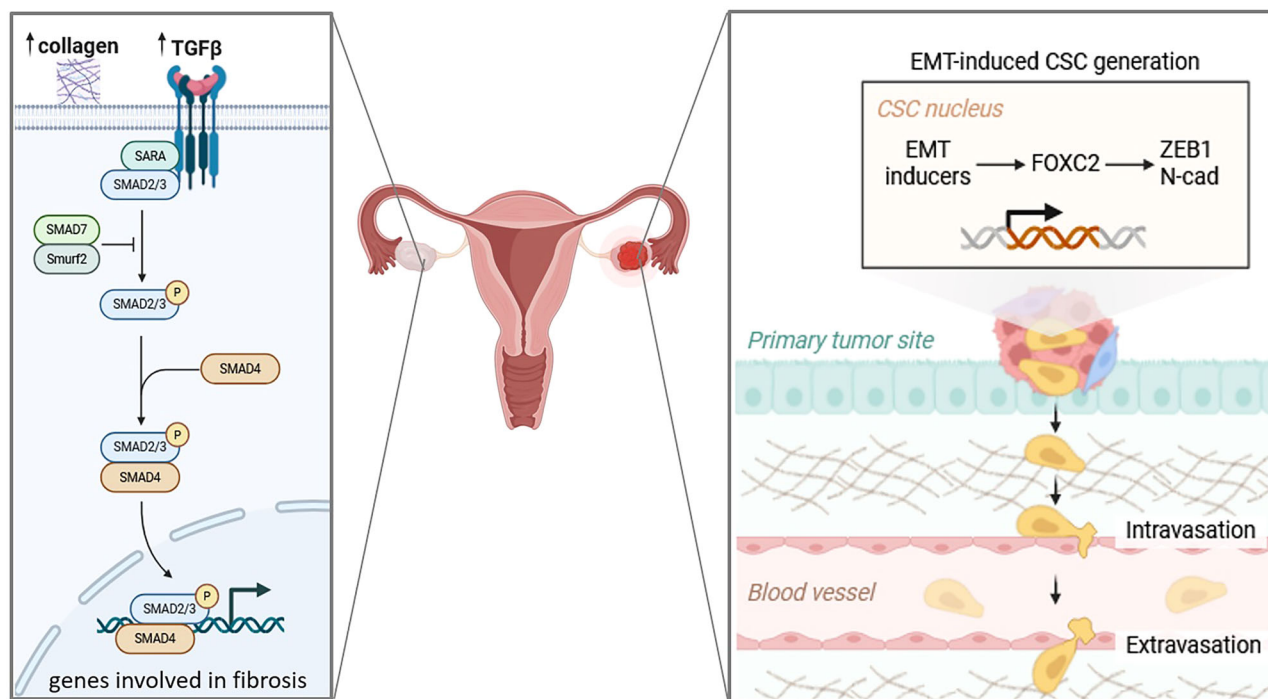


Fig. 2 | Scheme showing the epithelial-to-mesenchymal transition (EMT) and the intravasation of cancer stem cells (CSC) from the primary tumor site into the bloodstream and their extravasation. Metformin therapy lowers TGFβ2

expression, and in ovaries of postmenopausal women have higher TGFβ and collagen expression. Metformin causes the downregulation of genes involved in fibrosis and the creation of the premetastatic niche.

Table 1 | The role of sirtuin in the ovary and its relationship with age

Role in the ovary	Age-related changes	Key molecular pathways/functions
SIRT1 Regulates oocyte maturation, oxidative stress, apoptosis, and maintenance of granulosa cell quality ¹⁴⁹ .	.Decreased expression with age; lower levels correlate with deterioration in oocyte quality and mitochondrial function ^{91,150}	FOXO, p53, NF-κB, oxidative stress regulation, apoptosis pathways ¹⁵¹ .
SIRT2 .Participates in the control of cell division, spindle stability and deacetylation of α-tubulin ^{152,153}	.Reduced expression in aging oocytes; associated with increased risk of aneuploidy ^{154,155}	Cdk1/cyclin B, α-tubulin, cell cycle regulation, spindle organization ⁹ .
SIRT3 Regulates mitochondrial metabolism and protection against oxidative stress in oocytes ¹⁰ .	Declines with age; its loss impairs mitochondrial quality and increases oxidative damage ¹⁰ .	OXPHOS pathways, MnSOD deacetylation, ROS regulation ¹⁰ .
SIRT4 Participates in energy metabolism in mitochondria ¹³ .	No clear data on age-related changes ¹⁵⁶ , but low expression reported in ovarian cancer ¹⁴ . In contrast, higher levels were detected in older mice, and their knockdown restored normal spindle organisation ¹³ .	Modulation of PDHE1α subunit phosphorylation, Chromosome segregation ¹³ .
SIRT5 Regulates metabolic pathways through desuccinylation and demalonylation of mitochondrial proteins ¹⁵⁷ .	May be overexpressed in early ovarian tumorigenesis ¹⁶ , or reduce in women with reduced ovarian reserve ¹⁷ .	TCA cycle, ammonia detoxification, cisplatin resistance ¹⁶ .
SIRT6 Regulates oocyte maturation, cumulus cell expansion, and spindle organization ²⁰ .	Increased expression of SIRT6 in ovarian cancer indicates a better prognosis ¹⁴ .	DNA repair, gene expression via H3K9Ac and H3K56Ac, CDK1, cumulus expansion pathways ²⁰ .
SIRT7 Maintains genome stability, promotes chromosome synapsis and DNA repair in oocytes ¹⁹ .	Decreases with age; SIRT7 knockout leads to lower oocyte quality and higher aneuploidy ¹⁹ .	DNA repair (γH2AX, MLH1), H3K18Ac regulation, crossover control ¹⁵⁸ .

suggesting that SIRT1 does not directly control the phosphorylation of Smad2/3. However, one limitation of this observation is the experimental plan that involves immortalized cells which may have influenced the results, but it is possible that SIRT1 or resveratrol itself only indirectly affects TGF-β pathways by reducing oxidative stress, process clarified in the following paragraph^{50,51}. On the other hand, it has been found that in granulosa cells, TGF-β/Smad3 regulation is mediated by SIRT2 via Dickkopf deacetylation 1 (DKK1)⁹. DKK1 is a mediator of both cancerous and non-cancerous diseases, including fibrosis-depend diseases such as ischaemic heart

disease⁵². In polycystic ovary syndrome (PCOS), overexpression of DKK1 reduced the apoptosis rate of granulosa cells; moreover, overactivation of SIRT2 and increased deacetylation of DKK1 were detected in cells from PCOS rats. In confirmation of this, the SIRT2 inhibitor, AGK2, induced similar effects to DKK1 overexpression⁹.

Sirt6 levels, which also decline with age, guarantee adequate ovarian stroma development²². Indeed, SIRT6 knock-out mice show decreased expression of Plod1, the gene responsible for encoding the main collagen synthesizing enzyme, lysyl hydroxylase. Downregulation of lysyl

hydroxylase led to ovarian hypoplasia and reduced collagen fibre thickness²². This evidence corroborates the role of SIRT1s in ovarian fibrosis. Resveratrol treatment attenuates fibrinogen signaling and interstitial fibrosis by decreasing TGF- β , α -SMA, and type IV collagen deposition, thereby contributing to increased luteal cells and antral follicles⁵¹. Targets of the TGF- β /Smad2/Smad3 axis (Fig. 2), responsible for proliferation, migration, and differentiation, are also activated by induction of β -catenin nuclear translocation by TGF- β ⁵³. Stimulation of SIRT1 expression reduces β -catenin levels in androgen-induced fibrosis⁵¹.

Additionally, positive effects of metformin have been indicated in mice with ovarian fibrosis⁴⁴, ovarian fibrosis in postmenopausal women⁵⁴, and ovaries affected by PCOS⁵⁵. Metformin is an agonist with direct effects on SIRT1⁵⁶ and also AMP-activated protein kinase (AMPK)⁵⁷. The ovaries of postmenopausal women have higher TGF- β and collagen expression (Fig. 2), and the metformin administration reduces TGF- β 2 expression⁵⁴. In addition, metformin leads to the down-regulation of genes associated with fibrosis and pre-metastatic niche formation⁵⁴. A study in aged mice showed that metformin was effective in preventing fibrosis and less effective in curing fibrosis that occurred prior to supplementation⁴⁴. A study comparing the effects of metformin and resveratrol in mice with PCOS shows that both treatments do not affect the expression of SIRT1 and AMPK (target genes for resveratrol and metformin, respectively), yet equally improved ovarian structure with a consequent increase in corpus luteum and graft follicles⁵⁸. Those results indicate a key role for AMPK/SIRT1 signalling in counteracting ovarian fibrosis. There is a known relationship between AMPK and SIRT1, in which deacetylase is required for the activation of liver kinase B1 (LKB1), which phosphorylates the α -AMPK subunit. In the case of metformin, however, it has been shown that its anti-fibrotic effect is not related to an effect on the metabolism of abnormal ovarian fibroblast populations (highly active α -SMA-labelled) but rather modulates immune status⁴⁴ as it is described below. The greatest limit to the study of the association of SIRT1s with major fibrotic pathways, such as TGF- β , is still the scarce knowledge of the distribution and the age-related changes of TGF- β levels in the different ovarian cells, which can be very different based on the cell type⁵⁹.

Sirtuins and inflammation in ovarian fibrosis

Ovarian fibrosis is increasingly recognized as a hallmark of ovarian aging and pathology, including polycystic ovary syndrome (PCOS) and ovarian cancer. Fibrosis-related pathways are activated with age, particularly those associated with chronic inflammation. In aged ovarian tissue, there is notable upregulation of inflammatory mediators such as TNF- α , IL-1 β , IL-6, and components of the NLRP3 inflammasome^{37,44,60}. These cytokines are secreted not only by resident ovarian cells but also by infiltrating immune cells and senescent fibroblasts that exhibit a senescence-associated secretory phenotype (SASP)⁴⁴. The NF- κ B signaling pathway plays a central role in sustaining this inflammatory environment. It promotes the expression of proinflammatory genes and contributes to fibrotic remodelling by enhancing fibroblast activation. Importantly, fibroblasts isolated from aged ovaries show enrichment in NF- κ B pathway activity compared to those from young, non-fibrotic tissue⁴⁴. Similarly, the TGF- β pathway, which intersects with both NF- κ B and JAK/STAT signaling, contributes to fibroblast-to-myofibroblast transition and collagen deposition. STAT3, in particular, is activated by cytokines such as IL-6 and plays a critical role in both systemic fibrotic diseases and ovarian cancer^{61,62}. In addition to stromal alterations, the ovarian immune microenvironment undergoes age-related remodeling. Immunosenescence, characterized by a shift from CD4+ to CD8+ T cells and increased M2 macrophage polarization, contributes to a pro-fibrotic state^{63,64}. Chemokines such as CCL2 and CCL5, involved in leukocyte recruitment, are also upregulated with age³⁷. Multinucleated macrophages, another feature of aged ovaries, may serve as biomarkers of fibrotic progression⁶⁵. Sirtuins, particularly SIRT1, SIRT2, SIRT3, and SIRT7, modulate many of these inflammatory and fibrotic pathways. SIRT1 negatively regulates NF- κ B by deacetylating its p65 subunit, thereby reducing its transcriptional activity and dampening inflammation⁶⁶. Treatments that activate the AMPK/SIRT1 axis, such as myo-inositol and semaglutide,

have been shown to reduce inflammatory cytokines and fibrosis in PCOS models and aged ovaries^{45,67}. Likewise, resveratrol, a potent SIRT1 activator, decreases NF- κ B/p65 activity and alleviates ovarian inflammation^{58,68}. SIRT2 expression increases following nicotinamide mononucleotide (NMN) supplementation and is associated with reduced levels of NLRP3, IL-18, and IL-1 β in aged ovaries, indicating its anti-inflammatory potential⁶⁹. Furthermore, SIRT3 negatively correlates with STAT3 activity in ovarian cancer, suggesting a suppressive role in inflammation-driven tumorigenesis⁶². Lastly, SIRT7 has been shown to interact with both p65 and p50 subunits of NF- κ B, modulating its expression and activity in ovarian cancer cells²¹. Together, these findings highlight the interconnected roles of inflammatory pathways and sirtuins in the progression of ovarian fibrosis and inflammation. Understanding these interactions opens new avenues for therapeutic interventions targeting aging-related ovarian disorders.

These findings underscore the multifactorial nature of ovarian fibrosis, where chronic inflammation, immune system remodeling, and stromal cell activation converge to drive progressive fibrotic changes in aging ovarian tissue. Sirtuins emerge as key molecular regulators within this network, exerting anti-inflammatory and antifibrotic effects through modulation of NF- κ B, STAT3, and inflammasome signaling. Their interaction with metabolic pathways such as AMPK and their responsiveness to NAD+ availability suggest a broader role in linking energy status with immune and fibrotic responses. Continued investigation into the specific mechanisms by which distinct sirtuin isoforms influence these processes may yield novel insights into ovarian aging and identify potential molecular targets for therapeutic modulation in fibrotic and inflammation-associated ovarian disorders.

Sirtuins and oxidative stress in ovarian fibrosis

Ovarian fibrosis is a hallmark of reproductive aging and a common feature in pathological conditions such as premature ovarian insufficiency and polycystic ovary syndrome. One of the central mechanisms contributing to this fibrotic remodelling is oxidative stress (OS), which arises from an imbalance between the production of reactive oxygen species (ROS) and the cell's ability to detoxify them. ROS can damage lipids, proteins, and nucleic acids, and their accumulation in ovarian cells impairs mitochondrial function, disrupts hormonal signaling, and promotes the activation of fibrotic and inflammatory pathways.

A primary target of oxidative damage is telomeric DNA, which, due to its guanine-rich sequence and limited repair capacity, is especially susceptible to ROS-induced breaks. This damage activates the DNA damage response (DDR) via pathways involving γ H2AX, XRCC6, and PARP1, which are upregulated in aging ovaries⁷⁰⁻⁷³. Telomere shortening and dysfunction consequently promote cellular senescence and apoptosis^{74,75}, processes that drive tissue remodeling and fibrotic changes. Additionally, OS and DNA damage induces activation of p53, which transcriptionally regulates pro-apoptotic and pro-fibrotic genes, often through upregulation of CDKN1A (p21) and downregulation of the retinoblastoma protein (RB) pathway, leading to cell cycle arrest and promoting senescence-associated secretory phenotypes (SASP)⁷⁶. Another major contributor to fibrotic remodeling under OS is p66Shc, a redox enzyme that promotes mitochondrial ROS production and upregulates profibrotic markers such as α -SMA and NLRP3 inflammasome components⁷⁷. p66Shc levels increase with age and correlate with fibrosis in the ovary and other organs. Deletion of p66 in progeric mice (telomerase RNA component knockout mice) alleviates age-related phenotypes, indicating a potential role for p66 in the ageing process⁷⁸. Similarly, dysregulation of the Keap1/Nrf2 antioxidant pathway under prolonged OS limits the cellular ability to activate antioxidant genes such as HO-1, SOD2, and CAT. Normally, oxidative stress leads to dissociation of Nrf2 from Keap1, its nuclear translocation, and activation of antioxidant response elements (ARE), but this axis is impaired in several ovarian pathologies including PCOS⁷⁹⁻⁸¹. Mitochondrial dysfunction, another key element in fibrogenesis, is tightly coupled to cellular redox status. With aging, mitochondrial membrane potential and oxidative phosphorylation efficiency decline, NAD+ /NADH ratios drop, and ATP

production is reduced. This leads to an increase in mitochondrial ROS and subsequent oxidative damage, further driving fibrotic gene expression and cellular dysfunction^{82,83}.

In this context of pro-fibrotic and oxidative signaling, sirtuins act as crucial regulators that can suppress or reverse many of these pathological changes. These NAD⁺-dependent deacetylases respond to metabolic and redox status and coordinate protective mechanisms against OS and fibrosis. Among them, SIRT1, SIRT3, SIRT5, SIRT6, and SIRT7 have been most widely studied in ovarian tissue. SIRT1 regulates the DDR by deacetylating p53, thereby limiting its pro-apoptotic and pro-fibrotic activity^{5,6}. Under oxidative conditions, SIRT1 expression is upregulated as a compensatory response, and its activity is further enhanced by compounds like celastrol and melatonin, which reduce the levels and activation of γ H2AX, XRCC6, and PARP1^{84,85}. Moreover, the kinase TOPK promotes SIRT1 expression while repressing p53 acetylation, and its inhibition leads to apoptosis under inflammatory stress, indicating the importance of this regulatory axis in follicular survival^{86,87}. SIRT1 also suppresses p66Shc expression, thereby attenuating ROS generation and inflammasome activation. In models of hyperandrogenism-induced ovarian fibrosis, resveratrol treatment upregulates SIRT1, reduces p66Shc levels, and ameliorates fibrotic changes⁵¹. SIRT6 complements this function by repressing p66Shc promoter activity and deacetylating histone H3K9Ac, reducing transcription of pro-apoptotic and pro-fibrotic genes^{88–90}. SIRT3 and SIRT5, both localized in mitochondria, maintain mitochondrial integrity and redox balance. SIRT3 deacetylates and activates FOXO3a, which in turn upregulates antioxidant enzymes such as SOD2 and CAT^{91–94}. It also regulates PGC-1 α and TFAM, promoting mitochondrial biogenesis. In PCOS and aging models, SIRT3 expression is reduced, correlating with decreased antioxidant defense and increased fibrotic gene expression^{95–97}. Resveratrol and melatonin restore SIRT3 levels and improve mitochondrial function, reversing these pathological changes^{98,99}. SIRT5, through its desuccinylase activity, regulates mitochondrial enzymes involved in oxidative phosphorylation and supports redox homeostasis, although its specific role in ovarian fibrosis remains to be fully elucidated¹⁰⁰. SIRT7, although less extensively studied in the context of ovarian function, has emerged as a key regulator of mitochondrial homeostasis and resistance to oxidative stress. It promotes mitochondrial ribosomal protein expression, supports mitochondrial translation, and limits the accumulation of ROS¹⁰¹. Importantly, the miR-17-5p/SIRT7 axis is a key regulatory factor in the DNA damage response in the ovaries, and its influence has been shown to reduce OS and the levels of γ H2AX, XRCC6, and PARP1 activity⁸⁴. Reduced expression of SIRT7 with aging may thus contribute to mitochondrial decline and the establishment of a pro-fibrotic environment. The interaction between sirtuins and FOXO transcription factors is central to the cellular oxidative stress response. SIRT1 and SIRT3 promote FOXO1 and FOXO3a activity, enhancing resistance to oxidative damage and inhibiting apoptosis^{91–94}. Disruption of this interaction by miRNAs such as miR-132 and miR-181a leads to FOXO inactivation, increased apoptosis, and promotion of fibrotic and neoplastic changes^{91,102,103}. Sirtuins also influence the Nrf2 pathway. SIRT1 deacetylates Nrf2, facilitating its nuclear translocation and activation of antioxidant genes. Natural compounds such as icariin and resveratrol amplify this effect, enhancing the expression of protective enzymes like HO-1 and restoring redox balance in oxidative ovarian environments^{104–106}. Finally, declining NAD⁺ levels during aging limit sirtuin activity and thereby compromise antioxidant defenses and mitochondrial function. Supplementation with NAD⁺ precursors like nicotinamide riboside improves ovarian function by restoring NAD⁺ pools, increasing SIRT1 and SIRT3 expression, and improving mitochondrial energy metabolism^{47,48,95,107–109}.

Sirtuin-mediated pathways therefore intersect with multiple regulatory networks involved in oxidative stress, mitochondrial function, and the fibrotic remodeling of ovarian tissue. Their activity is tightly

linked to cellular energy status and redox balance, positioning them as dynamic sensors and modulators of homeostasis in the ovarian microenvironment.

Ovarian cancer and sirtuins

High-grade serous ovarian cancer (HGSOC) represents one of the most challenging and lethal forms of gynecological malignancies, characterized by its aggressive progression and often late-stage diagnosis.

Genetic predispositions play a crucial role in the etiology of HGSOC. As recently shown, the prevalence of HGSOC subtype-specific survival varies by race¹¹⁰. Mutations in the BRCA1 and BRCA2 genes are the most significant genetic factors associated with an increased risk of developing ovarian cancer. Women carrying BRCA1 mutations face a 39%–44% lifetime risk, while BRCA2 mutation carriers have an 11%–17% lifetime risk of developing ovarian cancer (American Cancer Society). Besides BRCA mutations, other genetic factors such as mutations in BRIP1, RAD51C, and the genes associated with Lynch syndrome (PMS2, MLH1, MSH2, and MSH6) also contribute to the risk profile for HGSOC^{111–113}. Familial aggregation of ovarian and other cancers, such as breast, pancreatic, melanoma, and colon cancers, in first-degree relatives, underscores the importance of genetic epidemiology in HGSOC. Understanding these genetic predispositions is essential for identifying high-risk individuals and implementing preventive measures such as genetic counselling and risk-reducing surgeries.

Environmental and lifestyle factors are also implicated in the epidemiology of HGSOC. Obesity, use of hormone replacement therapy (HRT), and reproductive history, including lower parity, lifetime number of ovulatory cycles, and infertility, have been identified as significant risk factors for developing ovarian cancer^{112,114}. While combined oral contraceptive use lowers the risk of HGSOC, the use of postmenopausal hormone therapy slightly increases the risk for HGSOC, highlighting the complex interplay between hormonal influences and cancer development^{112,115}. Dietary factors, and physical inactivity are additional lifestyle factors that may contribute to ovarian cancer risk. For instance, diets high in fats and low in fruits and vegetables are associated with higher cancer risk, while regular physical activity may offer protective benefits^{111,112}. Environmental exposures such as the use of talcum powder in the genital area and prolonged exposure to asbestos have also been studied for their potential to increase ovarian cancer risk^{111,112}. The incidence of epithelial ovarian cancer, particularly endometriosis-associated ovarian cancer such as clear cell carcinoma and endometrioid carcinoma, has markedly increased in Japan¹¹⁶. It has also been reported that clear cell carcinoma and endometrioid carcinoma frequently co-exist with endometriosis, suggesting that endometriosis is a possible precursor lesion for these types of ovarian cancer. Endometriosis, a chronic gynecological condition affecting approximately 176 million (~10%) women of reproductive age worldwide, is another common risk factor for some OC types¹¹⁷. In a recent study in which 450 906 patients with and without endometriosis were analyzed, a history of endometriosis conferred a 4.2-fold increased risk for ovarian cancer¹¹⁸. Noteworthy, patients suffering from ovarian endometriomas and/or deep infiltrating endometriosis showed a 9.7-fold higher risk when compared to counterparts without endometriosis (Fig. 3)¹¹⁸. However, the risk for endometriosis patients to develop high-grade serous ovarian cancers is lower (2.7%) than to develop other histotypes, such as, endometrioid (7.96%) or low-grade serous (8.12%) ovarian cancer¹¹⁸. Women suffering from endometriosis are concerned about the increased ovarian cancer risk, and endometriosis-associated ovarian cancer is challenging for clinicians¹¹⁸. Moreover, the aforementioned patients are suffering from pain, anxiety and depression, impacting their psychological and social functioning^{119,120}. Counselling programs for patients suffering from endometriosis should also be provided to test for specific gene mutations that could later in life cause the development of ovarian cancer^{117,118}. Recent bioinformatic analyses have revealed a significant molecular overlap between PCOS and ovarian cancer, suggesting that PCOS may serve as a precursor condition for some OC subtypes. A set of 128 differentially expressed genes was found to be common to

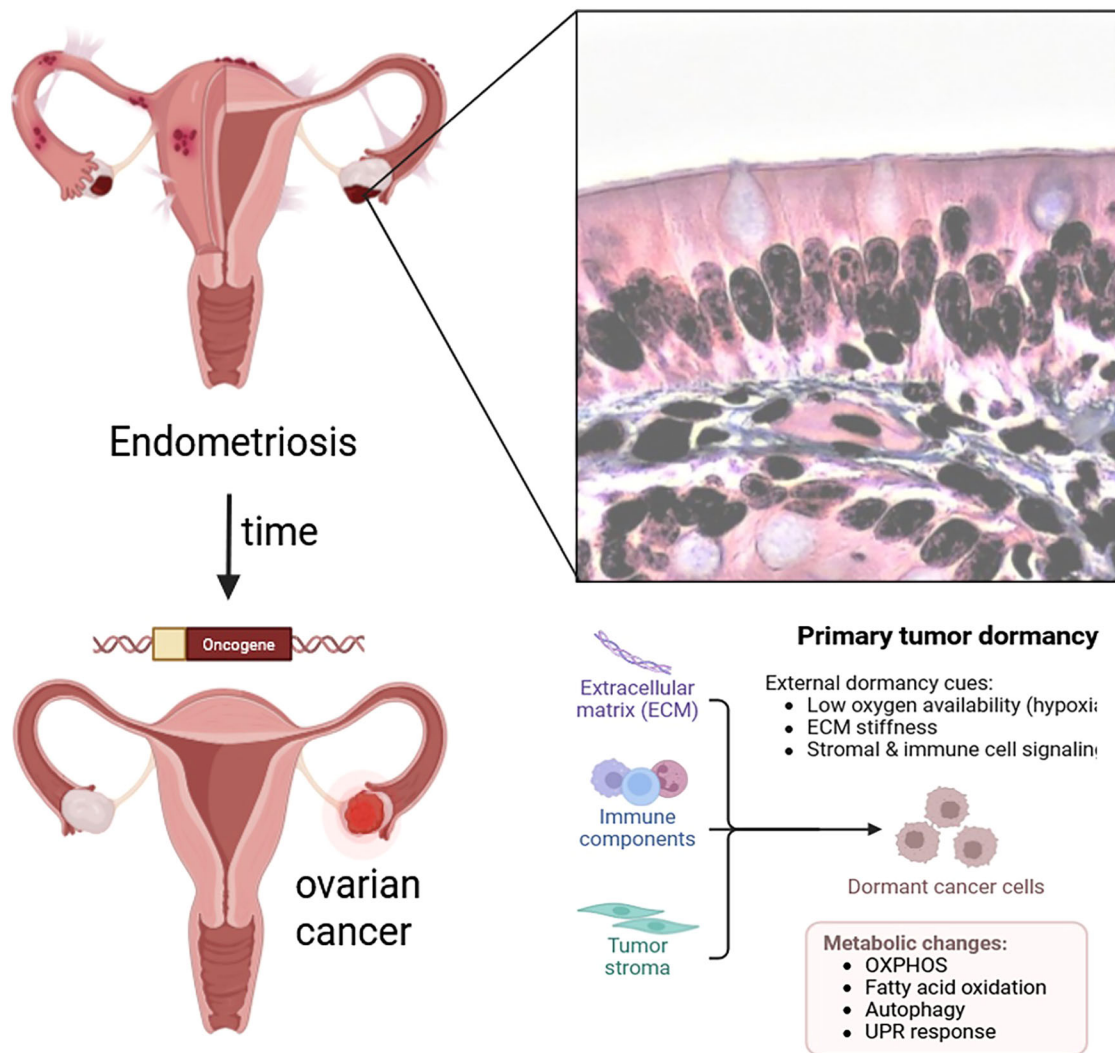


Fig. 3 | Scheme showing the development of ovarian endometriosis into ovarian cancer and the primary tumor dormancy.

both PCOS and OC, with particular emphasis on OGN (osteoglycin) as a potential biomarker linking the two¹²¹. Lower OGN expression, frequently observed in both PCOS and OC tissues, was associated with altered hormone signaling and poor prognosis, potentially promoting tumor progression through dysregulation of FSHR and m6A methylation. These findings imply that PCOS, particularly when marked by hormonal imbalance and genetic susceptibility, may contribute to the molecular pathogenesis of ovarian cancer¹²¹.

In the context of OC, the role of sirtuins remains an active area of investigation. SIRT1 functions as an oncogene as well as a tumor suppressor, regulating cell cycle progression, apoptosis, cell senescence, and oxidative stress resistance. Several studies have linked SIRT1 to cancer stemness and resistance to conventional therapy. SIRT1 has been shown to play a complex and often contradictory role in cancer development and progression¹²². One study revealed that SIRT1 expression was significantly decreased in OC tissues compared to normal ovarian tissues, and that lower SIRT1 levels were associated with more advanced disease stages and poorer patient survival¹²³⁻¹²⁵. In another, SIRT1 overexpression increases chemoresistance, tumorigenesis and epithelial-to-mesenchymal transition (EMT) phenotype^{126,127}. By extension, overexpression may promote a poorer prognosis for patients with OC^{11,123,128}. SIRT1 inhibition generally promotes the survival, proliferation, and metabolism of cancer cells, playing an important role in their resistance to treatment. However, MHY2245, a new SIRT1 inhibitor, by inhibiting the activity and expression of SIRT1, leads to

cell cycle arrest, apoptosis, and autophagy in cancer cells¹²⁹. Extracellular vesicles derived from cancer-associated adipocytes (CAA-EVs) play a crucial role in ovarian cancer progression by modulating the immune response and tumorigenesis¹³⁰. These vesicles carry SIRT1, which transcriptionally activates CD24 expression, leading to suppression of CD8 + T cell activity and promoting tumor immune escape¹³¹. Other studies indicate that SIRT1 plays a key role in inhibiting the progression of ovarian cancer by regulating the expression and acetylation of HMGB1. Importantly, overexpression of SIRT1 effectively reduced the migration and invasion of cancer cells and decreased angiogenesis, suggesting its therapeutic potential in the treatment of this aggressive disease¹³². Despite the original reports of an adverse effect of SIRT2 on OC prognosis¹³³, several recent studies have indicated that it is an OC suppressor^{11,123}. For example, lower expression of SIRT2 was associated with higher expression of cyclin-dependent kinase 4 (cdk4)¹³⁴, and SIRT2 overexpression had a favorable effect on the prognosis of OC patients¹²³. Metastatic spread is the main cause of death in epithelial ovarian cancer, yet the mechanisms remain unclear. Fn14 acts as a metastasis suppressor by inhibiting migration and invasion of EOC cells through downregulation of EMT¹³⁵. Mechanistically, Fn14 promotes acetylation-dependent degradation of Slug, a key EMT transcription factor, by interfering with SIRT2. Fn14 binds SIRT2, preventing its nuclear entry and thus reducing Slug deacetylation and stabilization¹³⁵. The third significantly down-regulated sirtuin in OC is SIRT3¹¹. Since tumorigenesis destabilizes the cell's energy economy, the role of SIRT3 may be crucial in OC. In one

recent study, SIRT3 transcript levels in various OC subtypes were significantly lower than in normal tissues¹²³. Moreover, as one of the most important proteins of mitochondrial metabolism, SIRT3, was identified as an independent favourable prognostic factor of OC¹³⁶. Interestingly, downregulated SIRT3 has also been detected in pre-metastatic tissue¹³⁷. SIRT3 is downregulated in metastatic ovarian cancer tissues and cells. Its knockdown enhances migration, invasion, and metastasis, while overexpression suppresses these processes. The mechanism involves inhibiting EMT by reducing the level of the protein Twist, with which SIRT3 directly interacts. The SIRT3/ Twist axis may represent a novel therapeutic target for metastatic ovarian cancer¹³⁸. Increased expression of mitochondrial proteins may occur in response to oxidative damage to cells in early tumorigenesis. SIRT5, which mainly acts in its territory, is also overexpressed in early tumorigenesis¹³⁹. In addition, SIRT5 increases OC resistance to cisplatin¹⁶. Mechanistically, it suppresses cisplatin-induced DNA damage by reducing reactive oxygen species through activation of the Nrf2/HO-1 antioxidant pathway, thereby contributing to chemoresistance in ovarian cancer¹⁶. In some types of liver cancer, SIRT5 depression limits disease progression¹⁴⁰. In ovarian cancer, reduction of SIRT5 expression, through upregulation of miR-27b-5p, reduced tumor progression in vitro¹⁴¹. The opposite dynamic is characterized by SIRT4, which maintains low escapes in OC^{123,142}, but SIRT4 overexpression adversely affects OC prognosis¹¹. The other sirtuins, nuclear SIRT6 and SIRT7, are lower in OC¹²³. This may indicate that their function is impaired and that genome stability and DNA repair processes are impaired, which is characteristic of tumorigenesis progression¹²³. Unfortunately, the results of other studies are inconclusive, on the one hand pointing to a suppressor character^{143,144} and on the other, promoting OC progression¹⁴⁵. Sirtuins, especially SIRT4 and SIRT6, play opposing roles in regulating ovarian cancer cell survival, making them potential competitive prognostic biomarkers. Bioinformatic analyses and immunohistochemical studies have shown that their high expression levels are associated with different prognoses and distinct impacts on tumor progression. SIRT4 is involved in the immune response during oocyte maturation, while SIRT6 participates in regulating mitochondrial processes and immune-related diseases, indicating their involvement in conflicting mechanisms influencing disease development¹⁴. In p53-mutant ovarian cancer, tumor cells under cisplatin treatment release exosomes containing the long non-coding RNA PANDAR (correlates with poor prognosis and promotes the development of cancer), which binds to the protein SRSF9¹⁴⁶. After translocation to the nucleus, SRSF9 suppresses apoptosis and modifies gene expression, leading to an altered mRNA ratio of SIRT4/SIRT6 that promotes cell survival and the development of cisplatin resistance. This mechanism enables tumor cells to rapidly adapt to treatment-induced stress, hindering therapeutic efficacy¹⁴⁷. Understanding this complex interaction between PANDAR, SRSF9, and sirtuins could open new therapeutic avenues for treating cisplatin-resistant ovarian cancers.

Conclusions

Sirtuins, through their extensive subcellular localization, exert important effects on energy (NAD⁺) metabolism, on which cellular functions depend, and influence key signaling pathways directly related to ovarian fibrosis (Smads, TGF- β). As we have presented, the kinetics of SIRT1 and SIRT3 are the best understood so far. However, this is not surprising because of their indisputable effects on Smads pathway gene transcription (in the case of SIRT1) and mitochondrial metabolism (in the case of SIRT3). In the case of the remaining members, we can expect similar functions to SIRT1 from SIRT6 and SIRT7, due to their similar localization. The same situation applies to SIRT3 and SIRT5. While the functions of SIRT2 and SIRT4 in the ovary remain underexplored, future studies could investigate their potential roles by drawing parallels with their known activities in other tissues, such as SIRT2's involvement in cell cycle regulation and microtubule dynamics, and SIRT4's role in mitochondrial metabolism and stress response.

What has been established is that inhibition of the major inflammatory and oxidative stress pathways NLRP3, NF κ B reduced

the expression of fibrosis markers (α -SMA) in ovarian tissue from aging mice, mice with induced fibrosis as well as ovarian tissue from postmenopausal women. In addition, sirtuins collaborate with key pathways that maintain mitochondrial fitness and biogenesis (PGC-1 α), and transcription factors (Nrf2, FOXO) that ensure adequate expression of antioxidant enzymes. As a separate observation, there is an interesting relationship between sirtuins and AMPK, which translates, for example, into modifications of the macrophage population, making it possible to discover the true causes of ovarian fibrosis. In the context of tumorigenesis, an interesting relationship has emerged between sirtuins and important fibrotic pathways for OC. Indeed, sirtuins can model the EMT process, a key process for metastasis and overexpression of sirtuins was able to reduce collagen deposition in ageing mice. While therapeutic agents like metformin (an AMPK and SIRT1 agonist) demonstrate potential in mitigating ovarian fibrosis, and resveratrol may offer even stronger SIRT1 activation, further research is needed to address limitations such as side effects and the scarcity of robust human clinical data supporting their efficacy and safety. The action of resveratrol is limited by its low bioavailability, and its interaction with other drugs (due to the inhibition of cytochromes P450) is still poorly understood¹⁴⁸. Metformin, on the other hand, can lead to numerous disorders of the digestive and endocrine systems¹⁴⁸.

Data availability

No datasets were generated or analysed during the current study.

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References

- Li, X. & Kazgan, N. Mammalian sirtuins and energy metabolism. *Int. J. Biol. Sci.* **7**, 575 (2011).
- Chen, M. et al. Research progress on Sirtuins (SIRT) family modulators. *Biomedicine Pharmacother.* **174**, 116481 (2024).
- Chalkiadaki, A. & Guarente, L. The multifaceted functions of sirtuins in cancer. *Nat. Rev. Cancer* **15**, 608–624 (2015).
- Yu, L. et al. The dual role of sirtuins in cancer: biological functions and implications. *Front Oncol.* **14**, 1384928 (2024).
- Park, J.-H. et al. TOPK inhibition accelerates oxidative stress-induced granulosa cell apoptosis via the p53/SIRT1 axis. *Int J. Mol. Med* **46**, 1923–1937 (2020).
- Park, S.-A., Joo, N.-R., Park, J.-H. & Oh, S.-M. Role of the SIRT1/p53 regulatory axis in oxidative stress-mediated granulosa cell apoptosis. *Mol. Med Rep.* **23**, 20 (2020).
- Inoue, T., Hiratsuka, M., Osaki, M. & Oshimura, M. The Molecular Biology of Mammalian SIRT Proteins: SIRT2 Functions on Cell Cycle Regulation. *Cell Cycle* **6**, 1011–1018 (2007).
- Zhang, H. et al. SIRT2 directs the replication stress response through CDK9 deacetylation. *Proc. Natl. Acad. Sci. USA* **110**, 13546–13551 (2013).
- Chen, L. & Kong, C. SIRT2-dependent DKK1 deacetylation aggravates polycystic ovary syndrome by targeting the TGF- β 1/Smad3 signaling pathway. *Gynecol. Endocrinol.* **40**, 2353733 (2024).
- Kordowitzki, P. Elucidating the Role of Sirtuin 3 in Mammalian Oocyte Aging. *Cells* **13**, 1592 (2024).
- Zeng, Z. et al. Gene expression and prognosis of sirtuin family members in ovarian cancer. *Medicine* **99**, e20685 (2020).
- Bergmann, L. et al. Subcellular Localization and Mitotic Interactome Analyses Identify SIRT4 as a Centrosomally Localized and Microtubule Associated Protein. *Cells* **9**, 1950 (2020).
- Zeng, J. et al. SIRT 4 is essential for metabolic control and meiotic structure during mouse oocyte maturation. *Aging cell* **17**, e12789 (2018).

14. Wang, H., Li, J., Huang, R., Fang, L. & Yu, S. SIRT4 and SIRT6 Serve as Novel Prognostic Biomarkers With Competitive Functions in Serous Ovarian Cancer. *Front. Genet.* **12**, 666630 (2021).
15. Kumar, S. & Lombard, D. B. Functions of the sirtuin deacylase SIRT5 in normal physiology and pathobiology. *Crit. Rev. Biochem. Mol. Biol.* **53**, 311–334 (2018).
16. Sun, X. et al. SIRT5 Promotes Cisplatin Resistance in Ovarian Cancer by Suppressing DNA Damage in a ROS-Dependent Manner via Regulation of the Nrf2/HO-1 Pathway. *Front. Oncol.* <https://doi.org/10.3389/fonc.2019.00754> (2019).
17. Pacella-Ince, L., Zander-Fox, D. L. & Lane, M. Mitochondrial SIRT5 is present in follicular cells and is altered by reduced ovarian reserve and advanced maternal age. *Reprod. Fertil. Dev.* **26**, 1072–1083 (2014).
18. Zhao, X. et al. NMN ameliorated radiation induced damage in NRF2-deficient cell and mice via regulating SIRT6 and SIRT7. *Free Radic. Biol. Med.* **193**, 342–353 (2022).
19. Vazquez, B. N., Blengini, C. S., Hernandez, Y., Serrano, L. & Schindler, K. SIRT7 promotes chromosome synapsis during prophase I of female meiosis. *Chromosoma* **128**, 369–383 (2019).
20. Cao, Z. et al. Cumulus cell-derived and maternal SIRT6 differentially regulates porcine oocyte meiotic maturation. *Theriogenology* **142**, 158–168 (2020).
21. Wang, H.-L. et al. SIRT7 Exhibits Oncogenic Potential in Human Ovarian Cancer Cells. *Asian Pac. J. Cancer Prev.* **16**, 3573–3577 (2015).
22. Li, L. et al. SIRT6 deficiency causes ovarian hypoplasia by affecting Plod1-related collagen formation. *Aging Cell* **23**, e14031 (2024).
23. Johnson, S. & Imai, S. NAD⁺ biosynthesis, aging, and disease. *F1000Res* **7**, 132 (2018).
24. Xie, N. et al. NAD⁺ metabolism: pathophysiologic mechanisms and therapeutic potential. *Sig Transduct. Target Ther.* **5**, 1–37 (2020).
25. Zhu, S. et al. The roles of sirtuins family in cell metabolism during tumor development. *Seminars in cancer biology*. Elsevier, 59–71 (2019).
26. Zhang, J. et al. Are sirtuins markers of ovarian aging?. *Gene* **575**, 680–686 (2016).
27. Amargant, F. et al. Ovarian stiffness increases with age in the mammalian ovary and depends on collagen and hyaluronan matrices. *Aging Cell* **19**, e13259 (2020).
28. Ouni, E. et al. Spatiotemporal changes in mechanical matrix components of the human ovary from prepuberty to menopause. *Hum. Reprod.* **35**, 1391–1410 (2020).
29. Landry, D. A., Vaishnav, H. T. & Vanderhyden, B. C. The significance of ovarian fibrosis. *Oncotarget* **11**, 4366–4370 (2020).
30. Naik, A. & Leask, A. Tumor-associated fibrosis impairs the response to immunotherapy. *Matrix Biol.* **119**, 125–140 (2023).
31. Herzog, B. H. et al. Tumor-associated fibrosis impairs immune surveillance and response to immune checkpoint blockade in non-small cell lung cancer. *Sci. Transl. Med.* **15**, eadh8005 (2023).
32. Zhang, Q., Wang, C. & Cliby, W. A. Cancer-associated stroma significantly contributes to the mesenchymal subtype signature of serous ovarian cancer. *Gynecologic Oncol.* **152**, 368–374 (2019).
33. Fujimoto, H. et al. Tumor-associated fibrosis: a unique mechanism promoting ovarian cancer metastasis and peritoneal dissemination. *Cancer Metastasis Rev.* **43**, 1037–1053 (2024).
34. Mazidimoradi, A. et al. The global, regional and national epidemiology, incidence, mortality, and burden of ovarian cancer. *Health Sci. Rep.* **5**, e936 (2022).
35. Ren, L.-L. et al. TGF- β as A Master Regulator of Aging-Associated Tissue Fibrosis. *Aging Dis.* **14**, 1633–1650 (2023).
36. Umehara, T. et al. Female reproductive life span is extended by targeted removal of fibrotic collagen from the mouse ovary. *Sci. Adv.* **8**, eabn4564 (2022).
37. Briley, S. M. et al. Reproductive age-associated fibrosis in the stroma of the mammalian ovary. *Reprod. (Camb., Engl.)* **152**, 245 (2016).
38. Tang, Z. et al. TIPE2 inhibits the migration and invasion of epithelial ovarian cancer cells by targeting Smad2 to reverse TGF- β 1-induced EMT. *FASEB J.* **38**, e70045 (2024).
39. Arend, R. C., Londoño-Joshi, A. I., Straughn, J. M. Jr & Buchsbaum, D. J. The Wnt/ β -catenin pathway in ovarian cancer: a review. *Gynecologic Oncol.* **131**, 772–779 (2013).
40. Du, F., Li, J., Zhong, X., Zhang, Z. & Zhao, Y. Endothelial-to-mesenchymal transition in the tumor microenvironment: Roles of transforming growth factor- β and matrix metalloproteins. *Heliyon* **10**, 1–13 (2024).
41. Aventaggiato, M. et al. Sirtuins and hypoxia in EMT control. *Pharmaceuticals* **15**, 737 (2022).
42. Isola, J. V. V. et al. A single-cell atlas of the aging mouse ovary. *Nat. Aging* **4**, 145–162 (2024).
43. Pangas, S. A., Li, X., Robertson, E. J. & Matzuk, M. M. Premature luteinization and cumulus cell defects in ovarian-specific Smad4 knockout mice. *Mol. Endocrinol.* **20**, 1406–1422 (2006).
44. Landry, D. A. et al. Metformin prevents age-associated ovarian fibrosis by modulating the immune landscape in female mice. *Sci. Adv.* **8**, eabq1475 (2022).
45. Khodir, S. A. et al. Diacerein and myo-inositol alleviate letrozole-induced PCOS via modulation of HMGB1, SIRT1, and NF- κ B: A comparative study. *Naunyn-Schmiedeberg's Arch Pharmacol.* <https://doi.org/10.1007/s00210-024-03497-7> (2024).
46. Tao, X., Cai, L., Chen, L., Ge, S. & Deng, X. Effects of metformin and Exenatide on insulin resistance and AMPK α -SIRT1 molecular pathway in PCOS rats. *J. Ovarian Res* **12**, 86 (2019).
47. Yang, Q. et al. Increasing ovarian NAD⁺ levels improve mitochondrial functions and reverse ovarian aging. *Free Radic. Biol. Med.* **156**, 1–10 (2020).
48. Yang, Q. et al. Deletion of enzymes for de novo NAD⁺ biosynthesis accelerated ovarian aging. *Aging Cell* **22**, e13904 (2023).
49. Guo, L. et al. Decrease in ovarian reserve through the inhibition of SIRT1-mediated oxidative phosphorylation. *Aging (Albany NY)* **14**, 2335 (2022).
50. Lan, D. et al. Trans-resveratrol inhibits phosphorylation of Smad2/3 and represses FSH β gene expression by a SirT1-independent pathway in L β T2 gonadotrope cells. *Reprod. Toxicol.* **32**, 85–92 (2011).
51. Wang, D. et al. Suppression of p66Shc prevents hyperandrogenism-induced ovarian oxidative stress and fibrosis. *J. Transl. Med.* **18**, 84 (2020).
52. Toth, P. P. Dickkopf-1: an emerging danger signal in hypertension and cardiovascular disease. *Eur. Heart J.* **45**, 704–706 (2024).
53. Zhou, B. et al. Interactions Between β -Catenin and Transforming Growth Factor- β Signaling Pathways Mediate Epithelial-Mesenchymal Transition and Are Dependent on the Transcriptional Co-activator cAMP-response Element-binding Protein (CREB)-binding Protein (CBP)*. *J. Biol. Chem.* **287**, 7026–7038 (2012).
54. McCloskey, C. W. et al. Metformin Abrogates Age-Associated Ovarian Fibrosis. *Clin. Cancer Res.* **26**, 632–642 (2020).
55. Mohiyiddeen, L. et al. Effects of low-dose metformin and rosiglitazone on biochemical, clinical, metabolic and biophysical outcomes in polycystic ovary syndrome. *J. Obstet. Gynaecol.* **33**, 165–170 (2013).
56. Cuyàs, E. et al. Metformin is a direct SIRT1-activating compound: computational modeling and experimental validation. *Front. Endocrinol.* **9**, 657 (2018).
57. Rena, G., Hardie, D. G. & Pearson, E. R. The mechanisms of action of metformin. *Diabetologia* **60**, 1577–1585 (2017).
58. Furat Rencher, S. et al. Effect of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS: an experimental study. *J. Ovarian Res.* **11**, 1–16 (2018).

59. Babayev, E. & Duncan, F. E. Age-associated changes in cumulus cells and follicular fluid: the local oocyte microenvironment as a determinant of gamete quality. *Biol. Reprod.* **106**, 351–365 (2022).
60. Lliberos, C. et al. Evaluation of inflammation and follicle depletion during ovarian ageing in mice. *Sci. Rep.* **11**, 278 (2021).
61. Chakraborty, D. et al. Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis. *Nat. Commun.* **8**, 1130 (2017).
62. Yang, Y. et al. Cryptotanshinone suppresses cell proliferation and glucose metabolism via STAT3/SIRT3 signaling pathway in ovarian cancer cells. *Cancer Med.* **7**, 4610–4618 (2018).
63. Isola, J. V. V. et al. Inflammation, immune cells, and cellular senescence in the aging ovary. *Reproduction* **168**, e230499 (2024).
64. Zhang, Z., Schlamp, F., Huang, L., Clark, H. & Brayboy, L. Inflammaging is associated with shifted macrophage ontogeny and polarization in the aging mouse ovary. *Reproduction* **159**, 325–337 (2020).
65. Foley, K. G., Pritchard, M. T. & Duncan, F. E. Macrophage-derived multinucleated giant cells: hallmarks of the aging ovary. *Reproduction* **161**, V5–V9 (2021).
66. Zhao, J. et al. Catalpol attenuates polycystic ovarian syndrome by regulating sirtuin 1 mediated NF- κ B signaling pathway. *Reprod. Biol.* **22**, 100671 (2022).
67. Liu, M. et al. Semaglutide Alleviates Ovary Inflammation via the AMPK/SIRT1/NF- κ B Signaling Pathway in Polycystic Ovary Syndrome Mice. *Drug Des. Devel Ther.* **18**, 3925–3938 (2024).
68. Han, Y., Luo, H., Wang, H., Cai, J. & Zhang, Y. SIRT1 induces resistance to apoptosis in human granulosa cells by activating the ERK pathway and inhibiting NF- κ B signaling with anti-inflammatory functions. *Apoptosis* **22**, 1260–1272 (2017).
69. Ma, Y. et al. Nicotinamide mononucleotide improves the ovarian reserve of POI by inhibiting NLRP3-mediated pyroptosis of ovarian granulosa cells. *J. Ovarian Res.* **17**, 236 (2024).
70. Ge, J. et al. SIRT6 participates in the quality control of aged oocytes via modulating telomere function. *Ageing (Albany NY)* **11**, 1965 (2019).
71. Valerio, D. et al. SA1/SA2 cohesion proteins and SIRT1-NAD⁺ deacetylase modulate telomere homeostasis in cumulus cells and are eligible biomarkers of ovarian aging. *Hum. Reprod.* **33**, 887–894 (2018).
72. Gao, M. et al. SIRT7 functions in redox homeostasis and cytoskeletal organization during oocyte maturation. *FASEB J.* **32**, 6228–6238 (2018).
73. Dang, Y. et al. MicroRNA-379-5p is associated with biochemical premature ovarian insufficiency through PARP1 and XRCC6. *Cell Death Dis.* **9**, 1–10 (2018).
74. Zhang, D. et al. Increased DNA damage and repair deficiency in granulosa cells are associated with ovarian aging in rhesus monkey. *J. Assist. Reprod. Genet.* **32**, 1069–1078 (2015).
75. Mah, L.-J., El-Osta, A. & Karagiannis, T. C. γ H2AX: a sensitive molecular marker of DNA damage and repair. *Leukemia* **24**, 679–686 (2010).
76. Engeland, K. Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ.* **29**, 946–960 (2022).
77. Zhao, Y. et al. p66Shc contributes to liver fibrosis through the regulation of mitochondrial reactive oxygen species. *Theranostics* **9**, 1510 (2019).
78. Giorgio, M. et al. The p66Shc knocked out mice are short lived under natural condition. *Ageing Cell* **11**, 162–168 (2012).
79. Kamel, A. S., El-Sayed, S. S. & El-Sayed, N. S. Sulforaphane's role in Redefining autophagic Responses in depression associated with polycystic ovarian syndrome: Unveiling the SIRT1/AMPK/LKB1 pathway connection. *Eur. J. Pharm.* **969**, 176477 (2024).
80. Xia, M. et al. p62 suppressed VK3-induced oxidative damage through Keap1/Nrf2 pathway in human ovarian cancer cells. *J. Cancer* **11**, 1299 (2020).
81. Adinolfi, S. et al. The KEAP1-NRF2 pathway: Targets for therapy and role in cancer. *Redox Biol.* **63**, 102726 (2023).
82. Di Emidio, G. et al. NAD⁺ Metabolism and Mitochondrial Activity in the Aged Oocyte: Focus on the Effects of NAMPT Stimulation. *Ageing Dis.* **15**, 2828–2851 (2024).
83. Zhao, H.-C. et al. Role of Sirt3 in mitochondrial biogenesis and developmental competence of human in vitro matured oocytes. *Hum. Reprod.* **31**, 607–622 (2016).
84. Ding, C. et al. Exosomal miRNA-17-5p derived from human umbilical cord mesenchymal stem cells improves ovarian function in premature ovarian insufficiency by regulating SIRT7. *Stem Cells* **38**, 1137–1148 (2020).
85. Martín-Ramírez, R. et al. Celastrol and melatonin modify SIRT1, SIRT6 and SIRT7 gene expression and improve the response of human granulosa-lutein cells to oxidative stress. *Antioxidants* **10**, 1871 (2021).
86. Zhang, L. et al. The role of T-LAK cell-originated protein kinase in targeted cancer therapy. *Mol. Cell Biochem* **477**, 759–769 (2022).
87. Joo, N.-R., Park, S.-A., Park, J.-H. & Oh, S.-M. TOPK inhibits TNF- α -induced granulosa cell apoptosis via regulation of SIRT1/p53. *Biochem Biophys. Res Commun.* **664**, 128–135 (2023).
88. Shen, C. et al. SIRT6 reduces the symptoms of premature ovarian failure and alleviates oxidative stress and apoptosis in granulosa cells by degrading p66SHC via H3K9AC. *Gynecol. Endocrinol.* **39**, 2250003 (2023).
89. Wu, S., Zhang, J., Peng, C., Ma, Y. & Tian, X. SIRT6 mediated histone H3K9AC deacetylation involves myocardial remodelling through regulating myocardial energy metabolism in TAC mice. *J. Cell. Mol. Med.* **27**, 3451–3464 (2023).
90. Liu, M. et al. Sirt6 deficiency exacerbates podocyte injury and proteinuria through targeting Notch signaling. *Nat. Commun.* **8**, 1–15 (2017).
91. Di Emidio, G. et al. SIRT1 signalling protects mouse oocytes against oxidative stress and is deregulated during aging. *Hum. Reprod.* **29**, 2006–2017 (2014).
92. Xu, G. et al. Melatonin Attenuates Oxidative Stress-Induced Apoptosis of Bovine Ovarian Granulosa Cells by Promoting Mitophagy via SIRT1/FoxO1 Signaling Pathway. *Int J. Mol. Sci.* **24**, 12854 (2023).
93. Sevgin, K. & Erguven, P. SIRT1 overexpression by melatonin and resveratrol combined treatment attenuates premature ovarian failure through activation of SIRT1/FOXO3a/BCL2 pathway. *Biochemical Biophysical Res. Commun.* **696**, 149506 (2024).
94. Pang, X., Cheng, J., Wu, T. & Sun, L. SIRT3 ameliorates polycystic ovary syndrome through FOXO1/PGC-1 α signaling pathway. *Endocrine* **80**, 201–211 (2023).
95. Di Emidio, G. et al. Methylglyoxal-Dependent Glycative Stress and Deregulation of SIRT1 Functional Network in the Ovary of PCOS Mice. *Cells* **9**, 209 (2020).
96. Di Emidio, G. et al. Regulatory Functions of L-Carnitine, Acetyl, and Propionyl L-Carnitine in a PCOS Mouse Model: Focus on Antioxidant/Antiglycative Molecular Pathways in the Ovarian Microenvironment. *Antioxidants* **9**, 867 (2020).
97. Jiao, L. et al. SIRT3 Regulates Levels of Deacetylated SOD2 to Prevent Oxidative Stress and Mitochondrial Dysfunction During Oocyte Maturation in Pigs. *Microsc. Microanalysis* **29**, 2149–2160 (2023).
98. Song, C., et al. Melatonin improves age-induced fertility decline and attenuates ovarian mitochondrial oxidative stress in mice. *Sci. Rep.* **6**, 35165 (2016).
99. Okamoto, N., Sato, Y., Kawagoe, Y., Shimizu, T. & Kawamura, K. Short-term resveratrol treatment restored the quality of oocytes in aging mice. *Ageing (Albany NY)* **14**, 5628 (2022).
100. Le, M. et al. The emerging role of lysine succinylation in ovarian aging. *Reprod. Biol. Endocrinol.* **21**, 38 (2023).

101. Raza, U., Tang, X., Liu, Z. & Liu, B. SIRT7: the seventh key to unlocking the mystery of aging. *Physiological Rev.* **104**, 253–280 (2024).
102. Zhang, M. et al. miR-181a increases FoxO1 acetylation and promotes granulosa cell apoptosis via SIRT1 downregulation. *Cell Death Dis.* **8**, e3088 (2017).
103. Cui, X., Jing, X., Liu, J., Bi, X. & Wu, X. miR-132 is upregulated in polycystic ovarian syndrome and inhibits granulosa cells viability by targeting Foxa1. *Mol. Med. Rep.* **22**, 5155–5162 (2020).
104. Chen, H. et al. The effect of icariin on autoimmune premature ovarian insufficiency via modulation of Nrf2/HO-1/Sirt1 pathway in mice. *Reprod. Biol.* **22**, 100638 (2022).
105. Cai, M. et al. Resveratrol attenuates hydrogen peroxide-induced injury of rat ovarian 1 granulosa-lutein cells by resisting oxidative stress via the SIRT1/Nrf2/ARE 2 signaling pathway. (2022)
106. Lu, C.-S. et al. The protective effects of icariin against testicular dysfunction in type 1 diabetic mice Via AMPK-mediated Nrf2 activation and NF- κ B p65 inhibition. *Phytomedicine* **123**, 155217 (2024).
107. Wang, X., Wang, L. & Xiang, W. Mechanisms of ovarian aging in women: a review. *J. Ovarian Res* **16**, 67 (2023).
108. Liang, Z., Qian, H., Yanxiao, Y. I., Shaoyang, J. I. & Mingwei, X. Wenshen Yangxue decoction promotes follicular development in aged female mice stimulation of the silent information regulator 3/ forkhead transcription factor O1 3a pathway. *J. Tradit. Chin. Med* **42**, 539–545 (2022).
109. Zhang, Q. et al. Mitochondrial and glucose metabolic dysfunctions in granulosa cells induce impaired oocytes of polycystic ovary syndrome through Sirtuin 3. *Free Radic. Biol. Med* **187**, 1–16 (2022).
110. Davidson, N. R. et al. Molecular subtypes of high-grade serous ovarian cancer across racial groups and gene expression platforms. *Cancer Epidemiology, Biomarkers & Prevention.* (2024)
111. Zamwar, U. M. & Anjankar, A. P. Aetiology, epidemiology, histopathology, classification, detailed evaluation, and treatment of ovarian cancer. *Cureus* **14**, (2022).
112. Webb, P. M. & Jordan, S. J. Global epidemiology of epithelial ovarian cancer. *Nat. Rev. Clin. Oncol.* **21**, 389–400 (2024).
113. Barnes, D. R. et al. Large-scale genome-wide association study of 398,238 women unveils seven novel loci associated with high-grade serous epithelial ovarian cancer risk. *medRxiv* (2024).
114. Trabert, B. et al. The risk of ovarian cancer increases with an increase in the lifetime number of ovulatory cycles: an analysis from the Ovarian Cancer Cohort Consortium (OC3). *Cancer Res.* **80**, 1210–1218 (2020).
115. Gjorgoska, M. & Rizner, T. L. From fallopian tube epithelium to high-grade serous ovarian cancer: A single-cell resolution review of sex steroid hormone signaling. *Prog. Lipid Res.* **96**, 101302 (2024).
116. Yamagami, W. et al. A retrospective study for investigating the relationship between old and new staging systems with prognosis in ovarian cancer using gynecologic cancer registry of Japan Society of Obstetrics and Gynecology (JSOG): disparity between serous carcinoma and clear cell carcinoma. *J. Gynecol. Oncol.* **31**, e45 (2020).
117. Fonseca, M. A. et al. Single-cell transcriptomic analysis of endometriosis. *Nat. Genet.* **55**, 255–267 (2023).
118. Barnard, M. E. et al. Endometriosis typology and ovarian cancer risk. *Jama* **332**, 482–489 (2024).
119. Mechsner, S. et al. Transcranial direct current stimulation to reduce chronic pelvic pain in endometriosis: phase II randomized controlled clinical trial. *Pain. Med.* **24**, 809–817 (2023).
120. Wu, C.-M. et al. Analysis of risk factors for postoperative anxiety and depression in endometriosis patients with reproductive intention. *World J. Psychiatry* **14**, 1364 (2024).
121. Zou, J. et al. Identification of key genes associated with polycystic ovary syndrome (PCOS) and ovarian cancer using an integrated bioinformatics analysis. *J. Ovarian Res* **15**, 30 (2022).
122. Alves-Fernandes, D. K. & Jasiulionis, M. G. The role of SIRT1 on DNA damage response and epigenetic alterations in cancer. *Int. J. Mol. Sci.* **20**, 3153 (2019).
123. Sun, X., Wang, S., Li, Q. Comprehensive Analysis of Expression and Prognostic Value of Sirtuins in Ovarian Cancer. *Front. Genet.* <https://doi.org/10.3389/fgene.2019.00879> (2019).
124. Wang, R.-H. et al. Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. *Cancer cell* **14**, 312–323 (2008).
125. Wilking, M. J. & Ahmad, N. The role of SIRT1 in cancer: the saga continues. *Am. J. Pathol.* **185**, 26–28 (2015).
126. Qin, J. et al. Hypoxia-inducible factor 1 alpha promotes cancer stem cells-like properties in human ovarian cancer cells by upregulating SIRT1 expression. *Sci. Rep.* **7**, 10592 (2017).
127. Mvunta, D. H. et al. Overexpression of SIRT1 is Associated With Poor Outcomes in Patients With Ovarian Carcinoma. *Appl. Immunohistochemistry Mol. Morphol.* **25**, 415 (2017).
128. Shuang, T., Wang, M., Zhou, Y. & Shi, C. Over-expression of Sirt1 contributes to chemoresistance and indicates poor prognosis in serous epithelial ovarian cancer (EOC). *Med Oncol.* **32**, 260 (2015).
129. Tae, I. H. et al. A new SIRT1 inhibitor, MHY2245, induces autophagy and inhibits energy metabolism via PKM2/mTOR pathway in human ovarian cancer cells. *Int J. Biol. Sci.* **16**, 1901–1916 (2020).
130. Storti, G. et al. Mesenchymal stem cells in adipose tissue and extracellular vesicles in ovarian cancer patients: a bridge toward metastatic diffusion or a new therapeutic opportunity?. *Cells* **10**, 2117 (2021).
131. Zheng, Q. et al. Delivery of SIRT1 by cancer-associated adipocyte-derived extracellular vesicles regulates immune response and tumorigenesis of ovarian cancer cells. *Clin. Transl. Oncol.* **26**, 190–203 (2024).
132. Jiang, W., Jiang, P., Yang, R. & Liu, D.-F. Functional role of SIRT1-induced HMGB1 expression and acetylation in migration, invasion and angiogenesis of ovarian cancer. *Eur. Rev. Med. Pharmacol. Sci.* **22** (2018).
133. Teng, C. & Zheng, H. Low expression of microRNA-1908 predicts a poor prognosis for patients with ovarian cancer. *Oncol. Lett.* **14**, 4277–4281 (2017).
134. Du, Y., Wu, J., Zhang, H., Li, S. & Sun, H. Reduced expression of SIRT2 in serous ovarian carcinoma promotes cell proliferation through disinhibition of CDK4 expression. *Mol. Med. Rep.* **15**, 1638–1646 (2017).
135. Wu, A. et al. Fn14 Controls the SIRT2-Mediated Deacetylation of Slug to Inhibit the Metastasis of Epithelial Ovarian Cancer. *Adv. Sci.* n/a:2501552.
136. Li, J., Yue, H., Yu, H., Lu, X. & Xue, X. Development and validation of SIRT3-related nomogram predictive of overall survival in patients with serous ovarian cancer. *J. Ovarian Res.* **12**, 47 (2019).
137. Xiang, X.-Y. et al. SIRT3 participates in glucose metabolism interruption and apoptosis induced by BH3 mimetic S1 in ovarian cancer cells. *Int. J. Oncol.* **49**, 773–784 (2016).
138. Dong, X., Jing, L., Wang, W. & Gao, Y. Down-regulation of SIRT3 promotes ovarian carcinoma metastasis. *Biochem. Biophys. Res. Commun.* **475**, 245–250 (2016).
139. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature.* **474**, 609–615 (2011).
140. Zhang, R. et al. SIRT5 Promotes Hepatocellular Carcinoma Progression by Regulating Mitochondrial Apoptosis. *J. Cancer* **10**, 3871–3882 (2019).
141. Ke, F. et al. LINC01234 regulates microRNA-27b-5p to induce the migration, invasion and self-renewal of ovarian cancer stem cells through targeting SIRT5. *Cell Cycle* **21**, 1020–1033 (2022).
142. Csibi, A. et al. The mTORC1 Pathway Stimulates Glutamine Metabolism and Cell Proliferation by Repressing SIRT4. *Cell* **153**, 840–854 (2013).

143. Hubbi, M. E., Hu, H., Kshitiz, Gilkes, D. M. & Semenza, G. L. Sirtuin-7 Inhibits the Activity of Hypoxia-inducible Factors *. *J. Biol. Chem.* **288**, 20768–20775 (2013).
144. Zhang, J. et al. The histone deacetylase SIRT6 inhibits ovarian cancer cell proliferation via down-regulation of Notch 3 expression. *Eur. Rev. Med. Pharmacol. Sci.* **19**, 818–824 (2015).
145. Bae, J. S. et al. SIRT6 Is Involved in the Progression of Ovarian Carcinomas via β -Catenin-Mediated Epithelial to Mesenchymal Transition. *Front. Oncol.* <https://doi.org/10.3389/fonc.2018.00538> (2018).
146. Pal, S., Garg, M. & Pandey, A. K. Deciphering the Mounting Complexity of the p53 Regulatory Network in Correlation to Long Non-Coding RNAs (lncRNAs) in Ovarian Cancer. *Cells* **9**, 527 (2020).
147. Wang, H. et al. Cisplatin-induced PANDAR-Chemo-EVs contribute to a more aggressive and chemoresistant ovarian cancer phenotype through the SRSF9-SIRT4/SIRT6 axis. *J. Gynecologic Oncol.* **35**, e13 (2023).
148. Shurrab, N. T. & Arafa, E.-S. A. Metformin: A review of its therapeutic efficacy and adverse effects. *Obes. Med.* **17**, 100186 (2020).
149. Alam, F. et al. Interplay between oxidative stress, SIRT1, reproductive and metabolic functions. *Curr. Res. Physiol.* **4**, 119–124 (2021).
150. Ilijas, J. D., Wei, Z. & Homer, H. A. Sirt1 sustains female fertility by slowing age-related decline in oocyte quality required for post-fertilization embryo development. *Aging Cell* **19**, e13204 (2020).
151. Salminen, A. et al. Interaction of aging-associated signaling cascades: Inhibition of NF- κ B signaling by longevity factors FoxOs and SIRT1. *Cell. Mol. life Sci.* **65**, 1049–1058 (2008).
152. Nagai, T., Ikeda, M., Chiba, S., Kanno, S. & Mizuno, K. Furry promotes acetylation of microtubules in the mitotic spindle by inhibition of SIRT2 tubulin deacetylase. *J. cell Sci.* **126**, 4369–4380 (2013).
153. Xu, D. et al. SIRT2 functions in aging, autophagy, and apoptosis in post-maturation bovine oocytes. *Life Sci.* **232**, 116639 (2019).
154. Qiu, D. et al. Sirt2-BubR1 acetylation pathway mediates the effects of advanced maternal age on oocyte quality. *Aging Cell* **17**, e12698 (2018).
155. Kim, H.-S. et al. SIRT2 Maintains Genome Integrity and Suppresses Tumorigenesis through Regulating APC/C Activity. *Cancer Cell* **20**, 487–499 (2011).
156. He, L. et al. SIRT4 in ageing. *Biogerontology* **24**, 347–362 (2023).
157. Park, J. et al. SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways. *Mol. cell* **50**, 919–930 (2013).
158. Vazquez, B. N., Thackray, J. K. & Serrano, L. Sirtuins and DNA damage repair: SIRT7 comes to play. *Nucleus* **8**, 107–115 (2017).

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