Acylation modifications regulate the ovarian microenvironment via metabolic reprogramming and protein relocalization (Review)

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Abstract. The ovarian microenvironment is the functional unit of follicular development, maturation, ovulation and steroid hormone production, and its homeostasis constitutes the cornerstone of female reproductive health. In recent years, protein acylation modification, a type of post-translational modification directly driven by intracellular metabolites, has attracted increasing attention for its role in the ovarian microenvironment. In the present study, the metabolic status that regulates the activity, stability and subcellular re-localisation of functional proteins by triggering changes in their acylation modification levels are systematically explained. This process bridges the metabolome, transcriptome and proteome, thereby remodelling the ovarian microenvironment, modulating polycystic ovary syndrome, premature ovarian insufficiency, ovarian aging or other related diseases. Additionally, it provides a theoretical foundation for developing novel diagnostic and therapeutic strategies targeting key modification enzymes or specific modification sites.

Contents

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1. Introduction

Post-translational modifications (PTMs) result in new chemical compositions and conformations due to the addition or removal of specific modification groups on the amino acid residues of proteins. PTMs occur frequently in proteins with notable structural or functional roles, such as secretory proteins, membrane proteins and histones (1). In recent years, with the application of high-performance liquid chromatography-tandem mass spectrometry, >650 types of PTMs have been identified to date, including methylation, phosphorylation, ubiquitination and glycosylation (2,3). Among these PTMs, protein lysine acylation modifications occupy a prominent role, as they can dynamically and flexibly install chemical marks on chromatin-associated proteins, thereby regulating chromatin state and a series of essential biological processes (4).

In the field of cell biology, a core proposition is to decipher how cells sense their internal metabolic status and adjust their functions and localisation accordingly. Compared with other PTMs, acylation modifications exhibit several unique characteristics. First, their substrates are directly derived from core cellular metabolic pathways, enabling modification levels to sense cellular metabolic status in real time, thus conferring metabolic sensitivity (5). Second, different types of acylation can compete or coordinate at the same residue site, forming a dynamic regulatory network and displaying network crosstalk (6). Third, acylation can be directly introduced during protein synthesis, breaking through the traditional scope of PTM and acting particularly on sites within the protein interior, thus showing unique regulatory mechanisms (7). These features make acylation modifications compatible with the ovarian microenvironment, which is metabolically active and functionally complex. Due to its ability to integrate both metabolic signals and functional instruction output, protein acylation modification play a marked role in the complex and dynamic ovarian microenvironment (8). The present review focusses on the pivotal role of acylation modification in reshaping the ovarian microenvironment at the epigenetic level via regulating metabolic reprogramming, key protein re-localisation and their precise interaction, aiming to provide new perspectives and potential targets for diagnosing and treating related diseases.

2. Overview of protein acylation modification

Based on the differences in the properties of modification groups, acylation modifications can be classified into three categories: i) Hydrophobic acylation modifications, including lysine acetylation (Kac), lysine propionylation (Kpr), lysine butyrylation (Kbu), lysine crotonylation (Kcr), lysine palmitoylation (Kpal) and lysine myristoylation (Kmyr); ii) polar acylation modifications, including lysine β-hydroxybutyrylation (Kbhb) and lysine 2-hydroxyisobutyrylation (Khib); and iii) acidic acylation modifications, including lysine malonylation (Kma), lysine glutarylation (Kglu), lysine succinylation (Ksucc), lysine lactylation (Kla) and lysine isonicotinylation (Kinic) (9). Among these, Kac, Kpr, Kbu, Kcr and Ksucc belong to short-chain acylation modifications, whereas Kglu, Kpal and Kmyr are classified as medium-to-long-chain acylation modifications (10). Notably, acylation can also occur in RNA, and N4-acetylcytidine (ac4C) modification is currently the only known form of RNA acylation (11).

Acylation modifications can be regulated through enzymatic or non-enzymatic mechanisms, with the enzymatic pathway being more common (12). Under enzyme-dependent conditions, acyltransferases ('writers') and deacylases ('erasers') counterbalance each other, transferring acyl groups, using acyl-coenzyme A (acyl-CoA) as the 'donor' substrate, to the modified proteins or RNA. Specific protein domains ('readers') mediate the execution of functions corresponding to acylation marks (8). In non-enzymatic systems, acyl-CoA is produced by the decomposition of microbial products or energy-rich substances such as glucose, fatty acids, amino acids and ketones. Abnormal metabolite accumulation directly triggers acylation (13,14) and this process exhibits a positive association with metabolite concentration (15). Therefore, intermediate metabolites possess non-traditional metabolic functions through direct acylation modification, serving as notable hubs among epigenetics, metabolome and proteome.

3. Overview of the ovarian microenvironment

Previous studies on ovarian function were primarily focused on the follicles alone; however, emerging research frontiers in recent years have revealed that ovarian function is collectively shaped by its 'seeds' (follicles) and 'soil' (ovarian microenvironment) (16-19). The ovarian microenvironment constitutes an integrated ecosystem composed of the core follicular unit consisting of oocytes, granulosa cells (GCs) and theca cells, the extracellular matrix (ECM), the immune system, vascular networks and other endocrine components including cytokines, metabolites, nerves and gonadotropins, steroid hormones and metabolism-related hormones (such as insulin and leptin) (20). The microenvironment provides nutritional support and mediates signal transduction for follicular growth and development, ovulation and corpus luteum formation. Crosstalk between follicles and the ovarian microenvironment directly determines follicular fate, thereby governing ovarian lifespan and fertility reserve (21).

Ovarian ECM. Dynamic reciprocity refers to the continuous bidirectional interaction between cells and their ECM-dominated microenvironment. Remodelling of the ECM exerts mechanical forces on cells and modifies biochemical mediators near the cell membrane, thereby initiating intracellular signalling cascades that are transmitted to the nucleus via the cell membrane and cytoskeleton, leading to changes in gene transcription and chromatin conformation (22,23). The main components of the ovarian ECM include collagen, elastin, fibronectin and laminin (24), which maintain the homeostasis and mechanical properties of ovarian tissue and provide physical support for follicular development (25).

Studies have shown that both the Hippo and phosphatidylinositol 3-kinase/protein kinase B (AKT)/mammalian target of rapamycin pathways are involved in the activation of primordial follicles in humans and mice, induced by mechanical forces on the ovarian ECM (26). During follicular development, when the angle of collagen fibres is <50˚, the ECM induces directional remodelling that ensures a higher degree of contact between fibres and maintains the stability of the ovarian topological structure (27). Before ovulation, the surge of luteinizing hormone (LH) stimulates antral follicles to degrade the connective tissue of the apical follicle via upregulating matrix metalloproteinases, leading to follicular rupture (28). During corpus luteum formation, type IV collagen is replaced by type I collagen, which also depends on precise periodic remodelling of the ECM (29).

In addition to supporting folliculogenesis, the ECM plays a notable role in ovarian reproductive dysfunction diseases. In polycystic ovary syndrome (PCOS), excessive deposition of ECM components and dense collagenisation aggravate ovarian tissue fibrosis, resulting in impaired follicular development, follicular atresia and ovulatory dysfunction (30). With ovarian aging, the levels of collagen, laminin and proteoglycans markedly, whereas the levels of elastin and fibronectin decrease (31). Coupled with the progressive accumulation of advanced glycation end products, the loss of ECM enzymatic hydrolysis required for tissue homeostasis (32) disrupts the assembly process of primordial follicles in patients with premature ovarian insufficiency (POI).

Acylation modifications can serve as sensors for mechanical stimulation. When the mechanotransduction signalling pathway is activated or inhibited, the acylation status of downstream target proteins changes correspondingly, thereby forming a regulatory feedback loop (33). Furthermore, mechanical stress treatment can globally elevate chromatin accessibility in mouse cumulus cells (CCs), which is accompanied by a markedly enhanced reprogramming efficiency of somatic cell nuclear transfer. This demonstrates that mechanotransduction can directly regulate the epigenetic state independent of metabolic changes and promote cell fate conversion (34).

Immune system. The main immune cells in the ovary include macrophages, T lymphocytes and B lymphocytes, among which macrophages are the most prominent type. Immune cytokines are mainly composed of tumour necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8 and transforming growth factor (TGF)-β (20). Macrophages play a marked role in ovarian physiological events such as follicular growth and development, ovulation, corpus luteum formation

and regression (35,36) Most related studies focus on the polarisation and dynamic transition of pro-inflammatory M1-type macrophages and tissue-remodelling M2-type macrophages (37-39).

Macrophages reside in the entire hypothalamic-pituitary-gonadal axis and play a notable role in hormonal output processes (such as ovulation, testosterone production, insulin resistance and adipokine release) and endocrine homeostasis (40). PCOS is characterised by systemic, chronic, low-grade inflammation and the ovarian tissue of patients with PCOS often show increased macrophage levels (41). A previous study showed that ovarian macrophages promote GC apoptosis and soluble CD163 secretion by upregulating the expression of the inflammatory marker CD163, which may be associated with the pathogenesis of PCOS (42). Through single-cell RNA sequencing of human ovaries, Zhou *et al* (43) identified four ovarian macrophage subtypes, namely C1QC+ tissue-resident macrophages (TRMs), HLA-DQA1+ TRMs, SPP1+ TRMs and VCAN+ monocyte-derived macrophages (MDMs). Functionally, the TRM subsets were mainly associated with immune regulation, tissue homeostasis and apoptotic cell elimination, whereas VCAN+ MDMs exhibited prominent inflammatory and pyroptosis-related features, thereby contributing to a pro-inflammatory microenvironment and exacerbating ovarian aging.

To date, there remains a research gap regarding how acylation modifications regulate the ovarian immune system through mechanisms involving metabolic reprogramming and protein relocalization, which could represent a promising direction for future investigation.

Vascular network. The ovarian vascular network is primarily composed of blood vessels and lymphatic vessels. Blood vessels provide oxygenation, transport hormonal nutrients, enable immune surveillance and clear waste products, whereas lymphatic vessels return extravascular fluid and proteins to the bloodstream and participate in immune cell transport (20). Small arteries extending to the cortical region activate the recruitment of dormant primordial follicles by increasing blood supply (44). When follicles reach the preantral stage, follicle-stimulating hormone (FSH) stimulates the surrounding theca cells to produce and release pro-angiogenic factors, leading to the formation of two concentric vascular networks (inner and outer) in the thecal sheath layer around the follicles (45). This active angiogenesis persists and reaches its peak in the mid-luteal phase (46).

Vascular endothelial growth factor (VEGF), particularly the proangiogenic isoforms VEGF120a and VEGF164a, together with VEGFR1, VEGFR2 and the soluble receptor sVEGFR2, contributes to the regulation of ovarian angiogenesis and thereby influences ovarian blood flow status during follicular development (47). Notably, VEGF exhibits opposite expression trends in PCOS and POI; VEGF levels are increased in the follicular fluid of patients with PCOS (48) but are decreased in the ovarian GCs of patients with POI (49). This suggests that VEGF may serve as a biomarker for predicting ovarian reserve function. Furthermore, VEGF polymorphisms may interfere with angiogenesis during embryo implantation, resulting in recurrent implantation failure (RIF) (50).

4. Mechanism of acylation modification in regulating the ovarian microenvironment: A discussion based on metabolic reprogramming and protein re-localisation

Research on metabolic reprogramming in cancer originated from the aerobic glycolysis phenomenon (also known as the Warburg effect) first proposed by Otto Warburg in the early 20th century; cancer cells preferentially utilise glycolysis rather than oxidative phosphorylation for energy even when oxygen is available (51). A comprehensive system was subsequently established for understanding metabolic reprogramming in the field of cancer research. Considering the ovary, in addition to the traditional energy metabolism processes such as lipid metabolism, glucose metabolism and oxidative metabolism (52), metabolic reprogramming places greater emphasis on the dynamic, forward-looking and function-driven remodelling of metabolic networks. Oogenesis, by nature, is stage-specific, encompassing the metabolic quiescence and maintenance of primordial follicles, metabolic state transition associated with selective follicle activation, metabolic coupling between oocytes and somatic cells and the preparation of metabolites preset for embryonic development (53). If the follicle unit can be analogised to a central 'production factory', the metabolic events of the ECM, blood vessels, immune system, hormones and other components serve as the peripheral 'logistics system', enabling the coordinated and efficient operation of signal transmission (inbound and outbound), raw material supply and structural support. The aforementioned scenarios indicate how metabolic reprogramming precisely regulates the ovarian microenvironment and balances the dual goals of developmental potential and static reserve.

Given that the still-limited ovarian-specific evidence for succinylation, crotonylation and malonylation in the regulation of the ovarian microenvironment, the present review focused primarily on acetylation, lactylation and palmitoylation in the subsequent discussion.

Central follicular unit

Metabolic quiescence and maintenance of primordial follicles. Histone deacetylase 6 (HDAC6) is notably expressed in most dormant primordial follicles. Its overexpression delays the activation rate of primordial follicles, thereby extending the reproductive lifespan of mice (54). Zhang *et al* (55) found that HDAC6 can directly act on the nerve growth factor (NGF) protein, downregulate the acetylation modification of NGF and accelerate its ubiquitin-mediated degradation. Low NGF expression levels maintain the metabolic quiescence of primordial follicles; conversely, reduced HDAC6 expression increases NGF expression, promoting the growth and development of primordial follicles, which provides clinical guidance for fertility preservation. In addition to HDAC6, forkhead box O3A (FOXO3A), a transcriptional regulator, can inhibit the excessive activation of primordial follicles by inducing cell cycle arrest when localised in the nucleus (56). The nuclear export of FOXO3A plays a marked role in POI pathogenesis (57); studies have shown that silent information regulator 1 (an NAD^+-dependent histone deacetylase)-mediated deacetylation of FOXO3A enhances its nuclear expression, maintains its nuclear localisation, inhibits excessive

activation of primordial follicles and anti-apoptosis, and thus protects ovarian reserve in mice (58). Mitochondrial alanyl-tRNA synthetase 2 (AARS2) is one of the key genes governing ovarian aging (59). By altering the mitochondrial targeting sequence, AARS2 mediates the hyperlactylation of carnitine palmitoyltransferase 2, a mitochondrial-associated protein, thereby inhibiting its enzymatic activity, leads to free fatty acid accumulation and the activation of peroxisome proliferator-activated receptor γ; this releases a large amount of lactic acid signals into the ovarian microenvironment, triggering FSH to initiate primordial follicle development and accelerating follicle exhaustion. Targeted inhibition of AARS2 can alleviate POI occurrence in mice (60).

The quiescence mechanism that protects the follicle pool is a double-edged sword; excessive metabolic quiescence inhibits the necessary cellular self-renewal, leading to DNA damage, organelle aging and errors in epigenetic marks. Oocyte aging is accompanied by an increase in reactive oxygen species (ROS) (21). Spindle assembly is a key step in oocyte maturation, and a well-formed spindle is an indicator for evaluating oocyte quality (61). During meiosis of aged oocytes, ROS-induced palmitoyl-protein thioesterase 1 (PPT1) localises to the spindle, and its overexpression causes tubulin depalmitoylation and spindle defects, resulting in decreased oocyte quality. However, melatonin rescues PPT-induced low palmitoylation state of aged oocytes (62).

Metabolic state transition accompanying follicle activation. Compared with young women with normal ovarian function, the expression levels of mitochondrial deacetylase SIRT3 and its target protein glutamate dehydrogenase (GDH) are decreased in GCs and CCs of women with diminished ovarian reserve or advanced age. The resulting hyperacetylation of GDH may reduce its enzymatic activity in granulosa and cumulus cells, thereby disturbing mitochondrial amino acid metabolism and compromising the metabolic support these follicular cells provide to the oocyte, which may contribute to an unfavorable follicular microenvironment (63). Follicular development relies on the dynamic proliferation of GCs; Zhou *et al* (64) proposed that the acetylation of lysine 27 on histone H3 (H3K27ac) induces the upregulation of growth differentiation factor-8, which in turn accelerates cell cycle transition from the G1 phase to the S phase through the activin-like kinase 5-extracellular signal-regulated kinase signalling pathway, thereby promoting GC proliferation. Another study found that when AGO2 formed a complex with the FOXO3 promoter, nuclear-enriched miR-195-5p upregulated FOXO3 expression in granulosa cells, likely through promoter-associated histone acetylation and demethylation, thereby influencing follicular development and atresia (65). Beyond the maintenance of nuclear localization, nucleocytoplasmic shuttling also serves a notable function in coupling metabolic status with follicular development. Lactylation of the transcription factor cAMP response element-binding protein (CREB) at residue K136 facilitates CREB phosphorylation, the assembly of the transcription complex and its translocation into the cytoplasm, thereby directly activating the transcription of genes implicated in granulosa cell proliferation and differentiation (66). This demonstrates that lactylation drives the subcellular relocation of key factors, transducing metabolic signals into transcriptional regulation to directly modulate granulosa cell function, thereby contributing to the remodelling of the ovarian microenvironment.

In patients with PCOS, metabolic pathways such as glycolysis, fatty acid β-oxidation, branched-chain amino acid catabolism and the tricarboxylic acid cycle are upregulated, whereas lactate dehydrogenase (LDH) activity is decreased in follicular fluid and serum. Abnormal levels of these intermediate metabolites exacerbate SIRT protein family dysfunction, leading to reduced downstream deacetylation activity. This further leads to mitochondrial dysfunction, redox imbalance and increased oxidative stress, which may disturb local intermediary metabolism, impair the metabolic and antioxidant support provided by cumulus and granulosa cells to the oocyte, and promote an inflammatory and metabolically unfavorable follicular microenvironment, thereby compromising follicle and oocyte development and reinforcing a vicious cycle (67-69). In addition to abnormalities in energy and oxidative metabolism, hyperandrogenism in PCOS alters CK2α nuclear translocation in granulosa cells, which is associated with increased HDAC2 phosphorylation, reduced H3K27ac and decreased expression of cell proliferation-related genes such as CCND1, CCND3 and PCNA, thereby disrupting normal follicular development (70). The desuccinylase SIRT5 is notably expressed in PCOS (71); silencing SIRT5 promotes GCs proliferation and inhibits their apoptosis by increasing the succinylation of GLI family zinc finger 1 protein at the lysine 232 site, suggesting that SIRT5 may be a new target for PCOS treatment (72). In premature ovarian failure (POF), ac4C modification of P16 mRNA is increased in ovarian granulosa cells. Electroacupuncture reduces ac4C modification of P16 mRNA, downregulates P16 and NAT10, upregulates CDK6 and CCND1, increases ovarian weight and peripheral estrogen levels, and decreases the proportion of atretic follicles in POF mice, thereby improving the follicular microenvironment associated with ovarian dysfunction (73).

Metabolic coupling between oocytes and somatic cells. During the window of follicular development, inhibition of histone deacetylases leads to increased levels of specific histone epigenetic marks. Specifically, this is characterised by increased levels of histone H3 lysine 9 acetylation (H3K9ac), H4ac and trimethylation of lysine at position 4 of histone H3 (H3K4me3), along with decreased H3K9me3 (74,75). This may result in inefficient and erroneous DNA repair, disrupting the transition from somatic cells to germline. Consequently, the number of primordial, primary and secondary follicles decreases, ultimately leading to the atrophy of ovarian oocyte reserve (76). The nuclear translocation of CK2α induced by the ovulatory signal LH or human chorionic gonadotropin (hCG) enhances HDAC2 activity. HDAC2 is preferentially localised in CCs and mural GCs adjacent to follicular fluid. Through the deacetylation of a series of non-histone proteins such as signal transducer and activator of transcription 3 and SMAD family member 7, it promotes the transcription of ovulation-related genes and the expansion of cumulus-oocyte complexes, thereby triggering ovulation (77). A recent study found that the overall protein acetylation level in the ovarian tissue of mice induced by a high-fat diet was markedly reduced (78). This negatively regulates the downstream phosphatase and

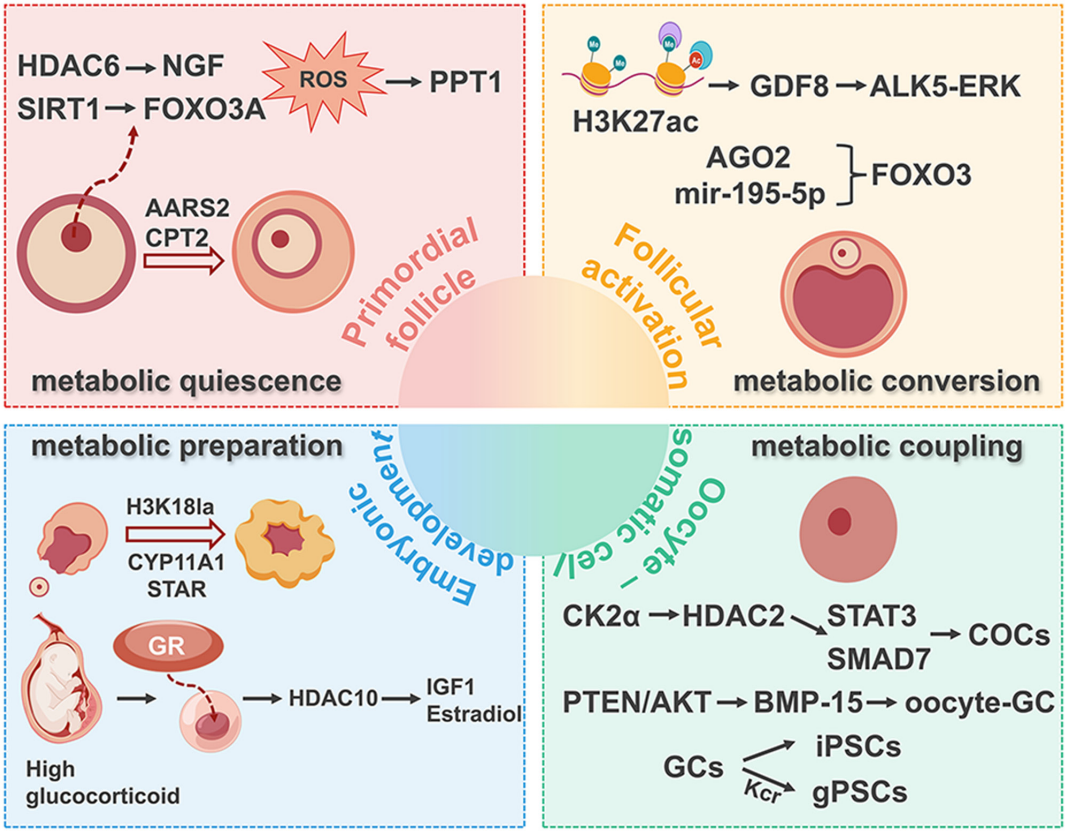

Figure 1. Mechanism of acylation modification regulating the central follicular unit. Oogenesis involves dynamic and prospective metabolic network remodeling, which can be summarized in four phases: Metabolic quiescence and maintenance of primordial follicles (acetylation, palmitoylation), metabolic state transitions accompanying follicle-selective activation (acetylation), metabolic coupling of oocyte-somatic cells (acetylation, crotonylation) and prepositioning of metabolites in preparation for embryonic development (acetylation, lactylation). Specific metabolic states in the ovarian microenvironment act as signaling molecules to influence the activities of acylation-modifying enzymes, thereby altering the expression levels and spatial conformations of key proteins, determining their intracellular localization and distribution, and ultimately triggering cell fate decisions. Achieving the dual goal of metabolic reprogramming in the ovarian microenvironment regulates and supports developmental potential and static reserve. NGF, nerve growth factor; PPT1, palmitoyl-protein thioesterase 1; AARS2, alanyl-tRNA synthetase 2; CPT2, carnitine palmitoyl transferase 2; GDF8, glutamate dehydrogenase 8; AGO2, argonaute 2; CK2α, casein kinase 2 alpha; COCs, cumulus-oocyte complexes; BMP-15, bonemorphogenetic protein-15; iPSCs, induced pluripotent stem cells; gPSCs, germline-competent PSCs; GR, glucocorticoid receptor; IGF1, insulin-like growth factor 1; HDAC6, histone deacetylase 6; FOXO3A, forkhead box O3A.

tensin homolog/AKT/FOXO3 signalling pathway, downregulates the expression of growth differentiation factor-9 and bone morphogenetic protein-15 and disrupts the normal operation of the oocyte-GC regulatory loop in the microenvironment.

Over the past decade, research on oocyte derivation has markedly advanced. Granulosa cells (GCs) can be reprogrammed into induced pluripotent stem cells (iPSCs) using only two transcription factors, Oct4 and Sox2, and this strategy has also contributed to advances in animal cloning research (79,80). GCs isolated from the ovaries of adult mice can be robustly induced to generate germline-competent PSCs (gPSCs) using purely chemical methods (81). These gPSCs can continuously and directionally differentiate into primordial germ cell-like cells, which further develop into functional oocytes. Thus, gPSCs modified by crotonylation and their derived germ cells exhibit longer telomeres and higher genomic stability, providing sufficient evidence for the safety and efficacy of chemical induction (81).

Presetting metabolite preparation for embryonic development. The accumulation of metabolites for embryonic development starts around the time of ovulation, continues through corpus luteum formation and concludes at the maternal-foetal interface. During the process of hCG-induced ovulation and corpus luteum formation, the hypoxic environment that is generated can stimulate lactate production. The accumulation of lactate leads to the lactylation of H3K18, which upregulates the transcription of cytochrome P450 family 11 subfamily A member 1 and steroidogenic acute regulator, thereby promoting the expression of luteinization markers in GCs (82). Liu *et al* (83) found that a maternal high-fat diet during pregnancy in mice causes mitochondrial dysfunction in the germ cells of offspring. However, vitamin B1 supplementation converts pyruvate into acetyl-CoA, which upregulates histone acetylation in the nuclei of GCs from newborn mice, increases the chromatin accessibility of promoters of cell cycle-related genes and enhances mitochondrial function in the GCs of the offspring. Maternal intrauterine exposure to high glucocorticoid levels forces the glucocorticoid receptor to translocate into the nucleus and upregulates the expression of HDAC10. This, in turn, reduces the H3K27ac level of insulin-like growth factor 1 and decreases oestradiol synthesis. This could potentially be the intrauterine origin mechanism underlying ovarian dysfunction and multi-organ developmental abnormalities in some offspring (84) (Fig. 1).

Table I. Potential acylation modification targets in ovarian-related diseases and their clinical transformation value.

Protein name	Protein type	Acylation function	Related diseases	Clinical target value
HDAC6	Eraser	Deacetylase	Ovarian aging	Maintain the metabolic quiescence of primordial follicles
SIRT1/3	Eraser	Deacetylase	Ovarian aging	Inhibit excessive activation of primordial follicles and anti-inhibit apoptosis
CPT2	Writer	Palmitoyltransferase	POI	Inhibit primordial follicle development
SIRT5	Eraser	Desuccinylase	PCOS	Accelerate GCs apoptosis
BRD4	Reader	Acetylation Reader	PCOS	Activate androgen receptor and accelerate ovarian fibrosis
HDAC5	Eraser	Deacetylase	PCOS	Inhibit ovarian angiogenesis and decrease ROS level
ZDHHC17	Writer	Palmitoyltransferase	PCOS	Convert androgens into oestrogens
HDAC10	Eraser	Deacetylase	Offspring multi-organ developmental abnormalities	Reduce IGF1 level and decrease oestradiol synthesis

HDAC, histone deacetylase; PCOS, poly cystic ovarian syndrome; ROS, reactive oxygen species; POI, premature ovarian insufficiency; GCs, granulosa cells; ZDHHC17, zinc finger DHHC-type palmitoyltransferase 17; BRD4, bromodomain-containing protein 4; CPT2, carnitine palmitoyl transferase 2.

Peripheral logistics system

ECM. The stiffness of the ECM restricts follicle expansion and oocyte maturation, keeping primordial follicles in a quiescent state. When growing follicles migrate to the ovarian medulla, they encounter a softer ECM, which expands their developmental space (85). Through transcriptome data analysis of GCs, Li *et al* (86) identified a cytoplasmically expressed trans-regulatory long non-coding RNA in actin gamma 1 (ACTG1) (TRLA). Mediated by H3K4ac, TRLA interacts with ACTG1 mRNA; it participates in follicular development by regulating GCs migration, increases oestrogen and progesterone secretion and promotes sexual maturation. In PCOS, the TGF-β/Smad signalling pathway upregulates the expression of the acetylation reader bromodomain-containing protein 4 (BRD4). BRD4 binds to histone 3/4 promoters to activate the androgen receptor, accelerating ovarian fibrosis; therefore, targeted inhibition of BRD4 is a promising intervention strategy (87).

Blood vessels. In the ovaries of mice with PCOS, the expression of histone deacetylase 5 (HDAC5) is compensatorily increased, accompanied by a state of high oxidative stress. HDAC5 overexpression downregulates the acetylation of VEGF receptor 2 (VEGFR2), inhibits the activation of the hypoxia-inducible factor-1α/VEGF factor A/VEGFR2 signalling pathway, reduces ovarian angiogenesis, improves abnormalities in ovarian morphology and serum hormone levels, decreases the level of ROS and increases the activities of catalase and superoxide dismutase. These findings reveal that HDAC5 exerts a protective role in PCOS by inhibiting ovarian angiogenesis, providing a candidate molecule for PCOS treatment (88).

Hormones. The S-palmitoylation modification of heat shock protein-90α mediated by zinc finger DHHC-type palmitoyltransferase 17 (ZDHHC17) generally upregulates the expression of CYP19A1. However, in the hyperandrogenic environment of PCOS, ZDHHC17 is downregulated, leading to impaired conversion of androgens to oestrogens and a vicious cycle of hyperandrogenism (89). The development of ZDHHC17-specific agonists may be beneficial for treating PCOS in the future (Table I).

Interplay between acylation modification and metabolic reprogramming in the ovarian microenvironment. In conclusion, in the regulation of the ovarian microenvironment, it is most accurate to summarize the relationship between acylation modification and metabolic reprogramming as a strong synergistic association with intertwined causality. First, Metabolic reprogramming alters the abundance and ratio of key metabolites such as acyl-CoA and succinyl-CoA, which serve as essential substrates or cofactors for acylation modifications (such as acetylation and succinylation) of proteins. In turn, acylation modification, acting as a rapid molecular switch, can directly regulate the activity, localization and stability of metabolic enzymes, thereby guiding metabolic pathways. Second, both acylation modification and metabolic reprogramming can be coordinated by upstream endocrine signals. In ovarian granulosa cells, FSH signaling can reshape histone H3 phosphorylation and acetylation, whereas metabolic reprogramming alters the availability of acyl-CoA metabolites that serve as donors for protein acylation. Conversely, acylation modification can regulate the activity, localization and stability of metabolic enzymes, thereby forming a bidirectional feedback loop between metabolism and acylation status (90-92). Furthermore, in diseases such as PCOS and POI/POF, abnormalities in acylation modification are frequently accompanied by metabolic disorders, including mitochondrial dysfunction and imbalances in glucose and lipid metabolism (73,93,94). These abnormalities jointly disrupt the ovarian microenvironment and represent different expressive levels of the same pathophysiological process.

The present review provides a conceptual framework for developing strategies to improve ovarian function and follicle quality, prevent adverse developmental outcomes in offspring and guide interventions for reproductive dysfunction-related

diseases. Paired homeodomain transcription factor-2 (PITX2) is one of the key factors promoting tumourigenesis and progression. A study showed that in ovarian cancer cells overexpressing PITX2, LDH-A is transiently localised in the nucleus and produces high concentrations of lactate (95). The accumulation of intranuclear lactate leads to decreased expression of HDAC1/2 and increased H3/H4ac, accelerating cancer cell proliferation. This suggests that targeting PITX2 or inducing the nuclear export of LDHA may be potential anti-cancer approaches. In drug-resistant ovarian cancer, under a lactate-accumulating microenvironment, Lu *et al* (96) found that niraparib resistance may involve the upregulation of H4K12 lactylation, which mediates the abnormal expression of RAD23 homolog A (RAD23A) via super-enhancers. This enhances the DNA damage repair capacity of ovarian cancer cells, indicating that RAD23A can serve as a potential therapeutic target.

Thus, targeting core proteins (such as transcription factors, signalling molecules and acylation-modifying enzymes) in the ovarian microenvironment or directionally inducing their re-localisation by intervening in any metabolic reprogramming pathway may represent an effective clinical therapeutic strategy in the future.

5. Conclusions

The present review systematically elaborates the role of protein lysine acylation modification, as a sensitive metabolic sensor, in the maintenance of ovarian microenvironment homeostasis and the occurrence of pathological disorders. It connects acylation modification and ovarian microenvironment at the cellular and molecular levels, proposes a relatively novel metabolic phenotype transition from oogenesis to embryonic development and identifies the regulatory mechanism of the interaction between metabolic reprogramming and protein re-localisation. However, current studies mostly rely on *in vitro* cell models, remaining limited to phenotypic association and preliminary functional verification, with inadequate mechanistic exploration. Additionally, research techniques related to novel PTMs are restricted, and clinical translation remains limited. In the future, it is essential to actively develop and apply technologies such as single-cell acylomics, construct advanced models more similar to the human ovarian microenvironment, identify specific acylation cycle molecules that can serve as diagnostic markers for ovarian dysfunction diseases and develop agonists or inhibitors targeting specific proteins. These efforts will help explore the potential of applying translational medicine to clinical practice.

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Availability of data and materials

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Authors' contributions

QX and YT conceived and designed the study; QX collected, analyzed and interpreted the data, and wrote the manuscript; and YT provided critical revisions for the intellectual content. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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