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Cross-Regulation Between DNA Methylation and Circadian Clock Reprogramming in Ovarian Cancer: Mechanistic Insights, Biomarker Potential, and Therapeutic Implications

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ABSTRACT

Early diagnosis remains challenging, recurrence rates remain high, and platinum resistance frequently develops in ovarian cancer (OC), collectively representing major barriers to long-term patient survival. DNA methylation (DNAm), as a relatively stable yet dynamically modifiable epigenetic signature, can capture alterations in tumor states and evolutionary trajectories associated with therapeutic pressure. Meanwhile, the circadian rhythm system regulates multiple cancer-related processes, including DNA damage repair, cell-cycle progression, metabolic adaptation, and immune microenvironment remodeling, thereby influencing OC development and treatment responses. Accumulating evidence suggests the existence of a bidirectional interplay between DNAm landscapes and the circadian clock network in OC. This review summarizes the emerging mechanisms underlying the crosstalk between DNAm and circadian reprogramming in OC, and further discusses their potential applications in early detection, prognostic stratification, dynamic monitoring of platinum resistance, and chronotherapy-based therapeutic strategies. Although current findings highlight the promising translational potential of the DNAm–circadian axis, its clinical implementation remains constrained by tumor heterogeneity, variations in sampling time points, cellular composition complexity, and insufficient validation across experimental models and clinical cohorts. Future integration of time-resolved sampling approaches, liquid biopsy platforms, single-cell and spatial epigenomic technologies, as well as prospective clinical trials evaluating circadian-guided interventions, may further define the translational boundaries and clinical utility of DNAm–circadian coupling in precision diagnosis and treatment of OC.

Abbreviations: AKT, protein kinase B; ARNTL, aryl hydrocarbon receptor nuclear translocator-like protein; BMAL1, brain and muscle ARNT-like 1; BRCA1, breast cancer 1; BRCA2, breast cancer 2; CA125, cancer antigen 125; CCGs, clock-controlled genes; cfDNA, cell-free DNA; CLOCK, circadian locomotor output cycles kaput; CpG, cytosine–phosphate–guanine; CRY, cryptochrome circadian regulator; CRY1, cryptochrome circadian regulator 1; ctDNA, circulating tumor DNA; DNAm, DNA methylation; DNMT, DNA methyltransferase; E-box, enhancer-box; EMT, epithelial–mesenchymal transition; FIGO, International Federation of Gynecology and Obstetrics; GEO, gene expression omnibus; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; HGSOC, high-grade serous ovarian cancer; HIF-1α, hypoxia-inducible factor-1 alpha; HPO, hypothalamic–pituitary–ovarian axis; HR, homologous recombination; HRD, homologous recombination deficiency; LH, luteinizing hormone; MBDs, methyl-CpG-binding domain proteins; MeCP2, methyl-CpG-binding protein 2; MYC, MYC proto-oncogene; NR3C1, nuclear receptor subfamily 3 group C member 1; OC, ovarian cancer; P4, progesterone; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor; PD, pharmacodynamic; PER, period circadian protein; PER2, period circadian regulator 2; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetic; RAD51C, RAD51 paralog C; SCN, suprachiasmatic nucleus; SIRT1, sirtuin 1; STAR, steroidogenic acute regulatory protein; TCGA, The Cancer Genome Atlas; TET, ten-eleven translocation dioxygenase; TF, transcription factor; TIMELESS, timeless circadian regulator; TTFL, transcription–translation feedback loop; 5hmC, 5-Hydroxymethylcytosine; 5mC, 5-Methylcytosine.

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1 | Introduction

Ovarian cancer (OC) is one of the most lethal malignancies of the female reproductive system, with poor outcomes largely driven by delayed diagnosis, recurrence, and drug resistance [1]. Current surveillance strategies based on imaging and CA125 remain inadequate for detecting occult disease, minimal residual disease, and emerging resistance [2, 3]. Although cytoreductive surgery followed by platinum-based chemotherapy provides initial responses, most patients eventually develop recurrence through complex evolutionary processes involving DNA damage repair, metabolic adaptation, microenvironment remodeling, immune evasion, and epigenetic reprogramming rather than isolated genetic events [4–6]. Therefore, multidimensional molecular approaches are required to capture tumor-state transitions and treatment adaptation.

DNA methylation (DNAm) represents a clinically relevant epigenetic layer in OC [7, 8]. Aberrant DNAm alterations occur early during tumorigenesis and regulate promoters, enhancers, DNA repair pathways, drug sensitivity, and cellular plasticity [9–12]. In HGSOC, extensive methylation remodeling is associated with therapeutic response, resistance, and prognosis [11, 13, 14]. Due to its stability, detectability, and reversibility, DNAm profiling in tumor tissues, cfDNA, and ctDNA holds potential for early detection, monitoring, and molecular stratification [15–17].

The circadian clock provides an additional temporal regulatory framework for OC biology by controlling cell cycle, DNA repair, metabolism, apoptosis, and immunity [18–21]. Dysregulated clock components are associated with proliferation, cisplatin sensitivity, prognosis, and immune characteristics [20–23].

Importantly, DNAm and circadian networks are interconnected through bidirectional regulation [24]. Epigenetic silencing of circadian genes, such as ARNTL (BMAL1) promoter methylation, impairs tumor suppression, cisplatin sensitivity, and circadian transcriptional activity [25–27], whereas circadian mechanisms can regulate dynamic DNAm patterns [28]. This review discusses the emerging interplay between DNAm and circadian regulation in OC and their potential implications for diagnosis, prognosis, resistance monitoring, and therapeutic optimization.

2 | Circadian Clock Networks in Normal Ovarian Function and OC

2.1 | Transcription–Translation Feedback Loops (TTFL) and Epigenetic Interfaces of Core Clocks

The circadian clock is an intrinsic timing system that coordinates mammalian physiological and behavioral processes through an approximately 24-h cycle and is synchronized by external zeitgebers such as light and feeding patterns [29]. Circadian rhythms are generated by the transcription–TTFL, which is closely integrated with chromatin accessibility, histone modifications, and rhythmic transcription factor binding [30, 31].

The CLOCK–BMAL1 (ARNTL) heterodimer activates PER, CRY, and clock-controlled genes (CCGs) through E-box binding, while PER/CRY-mediated negative feedback regulates circadian period, amplitude, and stability [32–40]. REV-ERB and ROR nuclear receptors further stabilize BMAL1 expression and connect circadian regulation with metabolism [41, 42].

Circadian transcription is highly dependent on epigenetic regulation. CLOCK-mediated histone acetylation, p300/CBP recruitment, and SIRT1-dependent deacetylation collectively regulate rhythmic chromatin states and transcriptional activity [43–45]. DNAm provides an additional stable regulatory layer that can maintain persistent circadian alterations [46, 47]. In cancer, BMAL1/ARNTL promoter CpG hypermethylation induces transcriptional repression, whereas BMAL1 restoration exerts tumor-suppressive effects [48, 49]. DNAm can impair transcription factor binding, recruit methyl-CpG-binding proteins, and promote repressive chromatin formation [50, 51]. Moreover, methylation of CpG-containing E-box motifs directly reduces CLOCK binding and alters TTFL outputs [52, 53]. Thus, aberrant DNAm may stabilize circadian disruption and contribute to circadian reprogramming in malignancies such as OC.

2.2 | Ovarian Temporal Homeostasis: From Steroidogenesis to the Ovulatory Window

The ovary is not merely an endocrine target organ; steroidogenesis, follicular maturation, and ovulation require precise temporal coordination between circadian rhythms and estrous-cycle regulation. This temporal homeostasis depends on integration of central circadian signals and ovarian peripheral clocks, which regulate steroidogenic activity and gonadotropin-driven events [54].

Circadian control of ovarian steroidogenesis involves rhythmic regulation of key steroidogenic genes. STAR, a clock-controlled gene containing E-box elements, interacts with CLOCK to establish circadian expression patterns during follicular development [55, 56]. In human luteinized granulosa cells, BMAL1 expression correlates with STAR, CYP11A1, and CYP19A1, and BMAL1 manipulation alters steroidogenic networks, indicating a role for local ovarian clocks in endocrine regulation [57]. Thus, circadian mechanisms establish temporal patterns of ovarian activity, while estrous-cycle signals further shape hormonal fluctuations [1, 58].

Reproductive function also depends on circadian gating within the hypothalamic–pituitary–ovarian (HPO) axis [59, 60]. Ovulation occurs within a restricted temporal window largely determined by circadian regulation of the preovulatory LH surge [54]. The SCN integrates circadian signals with estrogen feedback to regulate GnRH/LH secretion through mediators such as kisspeptin, while ovarian clocks modulate gonadotropin responsiveness and follicular–luteal transition [54, 61–67]. Conditional Bmal1 deletion in theca cells disrupts LH responsiveness, ovulation, and fertility, demonstrating the importance of ovarian clocks in reproductive timing [66]. Because ovulation involves inflammatory remodeling, oxidative stress, and DNA damage responses [68, 69], circadian disruption or epigenetic alterations may impair ovarian homeostasis and potentially contribute to epithelial injury and malignant transformation [70].

Collectively, ovarian temporal organization maintains reproductive homeostasis, and its disruption may link circadian

dysregulation, epigenetic alterations, and disease progression (Figure 1).

2.3 | Circadian Remodeling in OC: Network Disruption, Driving Mechanisms, and Heterogeneity

OC development is accompanied by extensive circadian network remodeling characterized by reduced oscillation amplitude, phase shifts, and cellular desynchronization rather than complete clock loss [19]. TCGA/GEO-based studies have identified associations between clock gene alterations, prognosis, and immune features; however, these relationships are strongly influenced by histological subtype, tumor purity, and microenvironmental composition, highlighting substantial heterogeneity [71]. For example, PER1 expression correlates with immune infiltration and clinical outcomes, suggesting that circadian dysregulation represents a context-dependent network rather than universal clock suppression [72]. Through regulation of cell cycle, DNA damage responses, and metabolism, circadian disruption may contribute to tumor progression and therapeutic tolerance, although causal mechanisms require further validation [73, 74].

Epigenetic remodeling is a key mechanism underlying circadian alteration in OC. Yeh et al. [27] demonstrated that ARNTL (BMAL1) promoter methylation and H3K27me3 enrichment occur in a subset of OC cells, while EZH2 inhibition restores ARNTL expression, suppresses tumor growth, enhances cisplatin sensitivity, and reestablishes rhythmic c-MYC activity. However, ARNTL/BMAL1 silencing is subtype- and context-dependent, consistent with the heterogeneous methylation landscape of OC [75].

Additionally, MYC-mediated repression of BMAL1/CLOCK/NPAS2 and HIF-1α–BMAL1 interactions under hypoxia further reshape circadian networks and metabolic adaptation [76, 77].

Moreover, single-cell and spatial studies reveal heterogeneous clock activity among tumor cells and microenvironmental components, emphasizing the need for cell-specific and time-resolved analyses [78]. Therefore, cell-specific and time-resolved approaches are required to define the functional consequences of circadian remodeling in OC.

3 | DNAm-Mediated Rewriting of the Circadian Clock

3.1 | Promoter CpG Island Hypermethylation: "Source Silencing" of Core Clock Transcription

Promoter CpG island hypermethylation is a well-established mechanism of long-term transcriptional repression in cancer epigenetics [79]. Accumulation of 5-methylcytosine (5mC) at

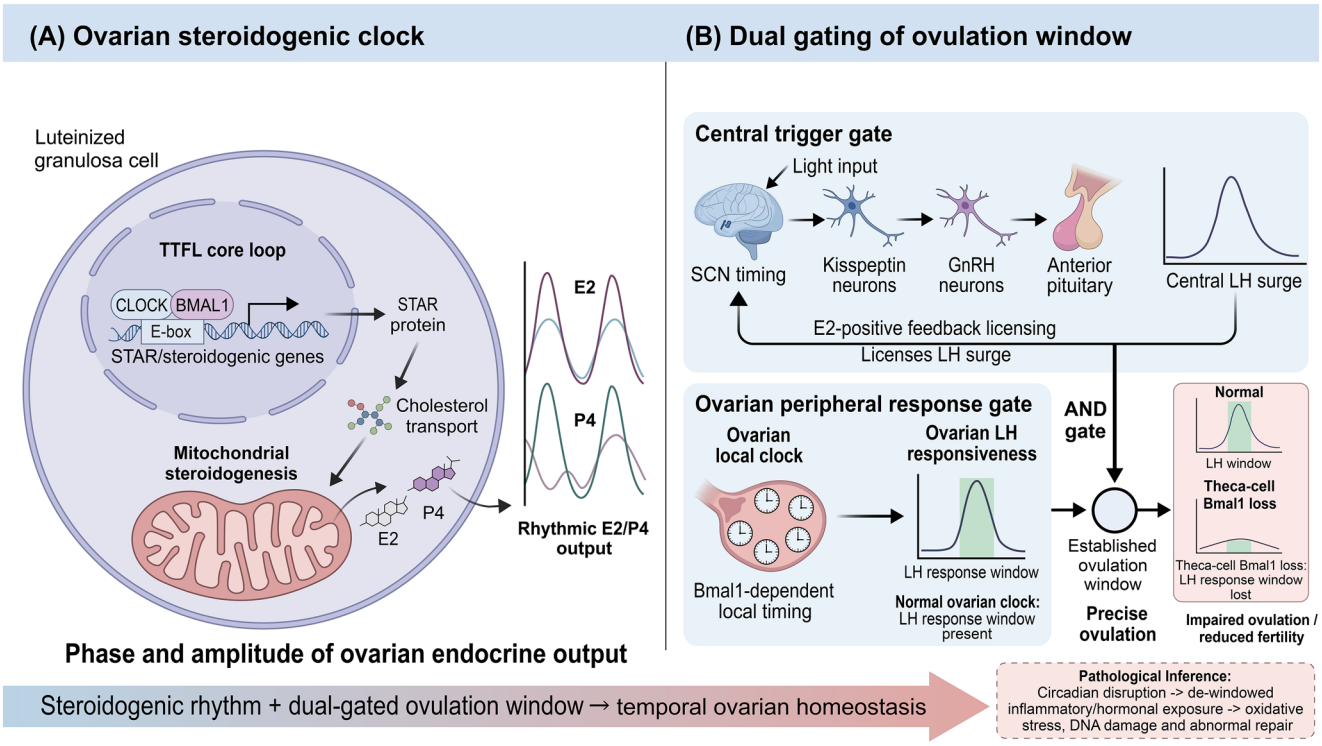


FIGURE 1 | Circadian regulation of ovarian steroidogenesis and ovulation timing. (A) Ovarian steroidogenic clocks regulate rhythmic hormone production. CLOCK:BMAL1-driven TTFL networks control steroidogenic gene expression, including STAR, promoting cholesterol transport, mitochondrial steroidogenesis, and rhythmic E2/P4 secretion in granulosa cells. (B) Dual circadian gating ensures precise ovulation timing. SCN-driven central signals regulate LH surge initiation, while ovarian Bmal1-dependent peripheral clocks establish LH responsiveness windows. Disruption of the ovarian clock impairs temporal coordination, leading to abnormal hormonal exposure, oxidative stress, and impaired ovarian homeostasis. BMAL1, brain and muscle ARNT-like 1; Bmal1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CYP11A1, cytochrome P450 family 11 subfamily A member 1; E2, estradiol; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; P4, progesterone; SCN, suprachiasmatic nucleus; STAR, steroidogenic acute regulatory protein; TTFL, transcription–translation feedback loop.

promoter regions of core clock genes can impair transcriptional initiation and recruit methylation readers such as MBDs and MeCP2, promoting histone deacetylation, repressive chromatin formation, and persistent clock gene silencing. These processes contribute to reduced circadian amplitude and cellular desynchronization in tumors [48, 51, 79–81].

In OC, promoter methylation alterations are closely associated with tumor progression, prognosis, and therapeutic resistance. Genome-wide methylation studies have identified extensive differences between cisplatin-sensitive and resistant OC cells, with some alterations reversible after demethylating treatment, supporting a role for DNAm in regulating resistance-associated transcriptional states [14]. Multi-omics analyses further indicate that circadian gene dysregulation is associated with survival and immune characteristics, suggesting a potential link between methylation-mediated clock regulation and therapy response [18]. PER2 represents a mechanistic example linking circadian regulation to platinum resistance. In cisplatin-resistant OC cells, PER2 downregulation is accompanied by promoter CpG hypermethylation, whereas PER2 restoration enhances cisplatin sensitivity, suppresses PI3K/AKT signaling, and reduces MDR1/MRP1 expression, implicating PER2 in drug efflux, apoptosis, and EMT regulation [82]. However, DNAm alterations may reflect persistent resistant states rather than acute drug responses, as platinum resistance involves widespread CpG changes, whereas short-term cisplatin exposure induces limited methylation and transcriptional alterations [83].

Notably, promoter hypermethylation does not universally silence clock genes, as its effects depend on methylation density, chromatin context, transcription factor accessibility, and additional epigenetic regulation [84]. Given the influence of tumor heterogeneity and cellular composition on methylation–expression relationships [85], the clinical significance of circadian gene methylation in OC requires further validation through subtype-specific and longitudinal studies (Figure 2).

3.2 | Cis-Regulatory Element (E-Box) Methylation: Loss of TF Occupancy and Binding Landscape Rewiring

CLOCK circadian transcription depends not only on core clock gene expression but also on phase-specific occupancy of genome-wide cis-regulatory elements [34]. E-box motifs (CANNTG, particularly CACGTG) serve as primary binding sites for CLOCK:BMAL1 and are widely distributed in promoter and enhancer regions. Under physiological conditions, CLOCK:BMAL1 recognizes these motifs within nucleosomal chromatin and promotes rhythmic transcription through coordinated interactions with chromatin components [34]. Structural studies further show that cooperative binding to paired E-box elements enhances DNA accessibility and contributes to robust circadian oscillations [34, 86].

DNAm within E-box motifs can alter transcription factor accessibility and binding affinity, thereby disrupting CLOCK transcriptional regulation [34, 50]. CACGTG-containing regions occupied by BMAL1:CLOCK are generally hypomethylated, whereas methylation of critical cytosines reduces CLOCK binding, suppresses transcriptional activation, and weakens circadian amplitude [87, 88]. Moreover, altered E-box methylation may reshape competition between CLOCK and other bHLH transcription factors, contributing to transcriptional rewiring [89].

In OC, circadian abnormalities associated with prognosis and immune features may reflect altered CLOCK regulatory activity rather than complete clock gene silencing [1, 18]. This mechanism may be particularly relevant in HGSOC, where MYC amplification or gain can enhance competition for E-box-containing regulatory regions [90]. MYC further suppresses circadian activity through REV-ERB induction and MYC–MIZ1-mediated repression of BMAL1 and CLOCK, weakening circadian oscillations and altering clock–cell-cycle interactions [76]. Therefore, methylation changes at E-box motifs and adjacent regulatory regions may function as context-dependent modulators of transcription factor binding, driving circadian rewiring during OC progression or therapeutic stress and contributing to heterogeneous clinical and immune phenotypes [1, 18] (Figure 2).

3.3 | Distal Enhancer Methylation: Topological Rewiring of Spatiotemporal Transcriptional Networks

Distal enhancers are essential cis-regulatory elements that regulate gene transcription through long-range enhancer–promoter interactions mediated by three-dimensional chromatin organization and coordinated transcription factor recruitment [18, 91]. Genome-wide studies have shown that CLOCK exhibits phase-specific binding across enhancer regions, accompanied by rhythmic changes in chromatin accessibility, H3K27ac enrichment, and transcriptional activity, indicating that circadian outputs are largely governed by dynamic distal regulatory networks [31, 92].

DNAm at enhancers functions as a regulator of regulatory network architecture rather than a simple gene switch. Methylation changes at enhancer-associated CpG regions can alter chromatin accessibility, transcription factor binding, cofactor recruitment, and enhancer–promoter communication through regulators such as CTCF [93, 94]. Temporal methylation patterns correlate with chromatin accessibility dynamics, and rhythmic demethylation of specific CpG regions can cooperate with enhancers to regulate clock-controlled gene expression, highlighting the role of DNA modifications in circadian enhancer regulation [28, 95–98].

In OC, distal enhancer remodeling contributes to adaptive malignant states. Shang et al. demonstrated that cisplatin exposure induces new distal enhancers and super-enhancer landscapes in platinum-resistant OC models, sustaining resistance-associated transcriptional programs [99]. Therapy-induced enhancer networks may further promote stemness and resistance phenotypes, while HGSOC methylome studies indicate that regional methylation patterns are associated with chemotherapy tolerance and poor outcomes [14, 100].

Because enhancers encode temporal regulatory information, their remodeling may influence circadian outputs by altering CLOCK recruitment and regulatory connectivity without

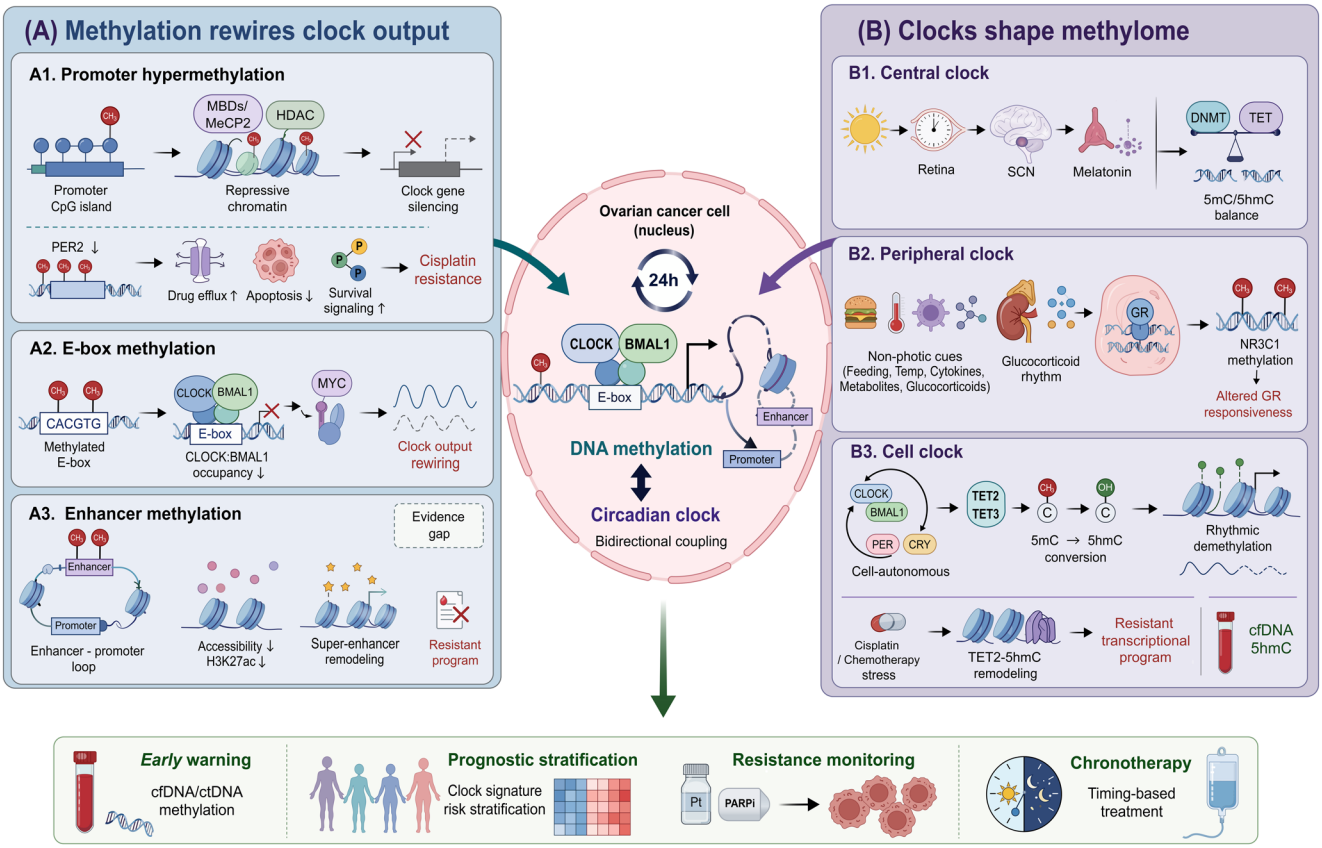


FIGURE 2 | Bidirectional DNA methylation–circadian clock regulation in ovarian cancer progression and therapy response. (A) DNA methylation reshapes circadian clock outputs in ovarian cancer. Promoter, E-box, and enhancer methylation alters CLOCK:BMAL1 transcriptional activity, induces clock gene silencing and chromatin remodeling, and contributes to resistant phenotypes through transcriptional rewiring. (B) Circadian clocks regulate DNA methylome dynamics. Central, peripheral, and cellular clocks influence DNMT/TET-mediated methylation remodeling through hormonal and metabolic cues, while chemotherapy stress further alters epigenetic states. This bidirectional coupling provides potential biomarkers for risk stratification, resistance monitoring, and chronotherapy. 5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; cfDNA, circulating cell-free DNA; CpG, cytosine–phosphate–guanine; ctDNA, circulating tumor DNA; DNMT, DNA methyltransferase; GR, glucocorticoid receptor; H3K27ac, histone H3 lysine 27 acetylation; HDAC, histone deacetylase; MBDs, methyl-CpG-binding domain proteins; MeCP2, methyl-CpG-binding protein 2; MYC, MYC proto-oncogene; NR3C1, nuclear receptor subfamily 3 group C member 1; PARPi, poly(ADP-ribose) polymerase inhibitor; TET, ten-eleven translocation methylcytosine dioxygenase.

complete clock gene silencing [92, 101]. Therefore, enhancer remodeling in OC may alter CLOCK:BMAL1 recruitment and circadian output connectivity without requiring complete silencing of core clock genes [99].

However, whether resistance-associated enhancers exhibit circadian oscillation or methylation-dependent regulation remains unclear. Integrated analyses of enhancer landscapes, circadian profiling, and methylomes are required to define this potential regulatory axis (Figure 2).

4 | How the Circadian Clock Shapes the DNAm Landscape

4.1 | The Central Clock as a System-Level Epigenetic Memory

The mammalian circadian system is hierarchically organized, with the suprachiasmatic nucleus (SCN) acting as the central pacemaker that synchronizes peripheral clocks through systemic outputs rather than directly regulating tumor cells [102]. In OC, the central clock shapes the temporal environment of peripheral tissues and the tumor microenvironment through regulation of sleep–wake rhythms, body temperature, behavioral activity, and melatonin secretion [19].

Night-shift work and nocturnal light exposure are major disruptors of circadian entrainment. Although Bhatti et al. [70, 103] reported an association between night-shift work and increased risk of aggressive epithelial OC and borderline ovarian tumors, subsequent meta-analyses showed no consistent overall association, likely due to differences in exposure assessment, shift duration, chronotype, subtype, and confounding factors. Melatonin represents a key interface between light signaling and tumor biology. Circadian disruption reduces nocturnal melatonin secretion, and lower melatonin levels have been observed in OC patients [104–106]. Experimental studies indicate that melatonin may inhibit OC progression through regulation of proliferation, apoptosis, oxidative stress, cell-cycle control, and immune responses [107–110]. It may also influence DNAm through DNMT/TET pathways

and 5mC/5hmC regulation [111, 112]. However, a direct causal link between central circadian disruption, melatonin-mediated epigenetic remodeling, and OC progression remains unproven. Integrated studies combining circadian exposure assessment, melatonin profiling, and multi-omics analyses are required to clarify this potential mechanism (Figure 2).

4.2 | Peripheral Clocks Translate Non-Photonic Cues Into Tissue-Specific Methylation Baselines

Peripheral clocks are continuously reset by non-photic zeitgebers, including feeding patterns, metabolic signals, inflammation, temperature changes, and glucocorticoids [113, 114]. Glucocorticoid signaling represents a major peripheral entrainment pathway, rapidly shifting clock gene expression in peripheral tissues while exerting limited effects on SCN rhythms [115]. In humans, hydrocortisone administration alters PER2, PER3, and BMAL1 expression phases in PBMCs without substantially affecting central circadian markers [116]. Beyond phase resetting, these signals influence metabolic and stress environments and may shape epigenetic states, with DNAm potentially serving as a molecular record of temporal and physiological conditions [43, 117].

In OC, glucocorticoid-mediated circadian regulation may depend on the expression and chromatin accessibility of the glucocorticoid receptor (GR), encoded by NR3C1. Aberrant NR3C1 promoter methylation has been identified in OC, and independent cohorts have linked NR3C1 methylation with cortisol-related phenotypes [9, 118–120]. Thus, NR3C1 methylation may function as an epigenetic threshold regulating glucocorticoid responsiveness and contribute to interindividual differences in circadian adaptation during tumor progression and treatment. Further integration of glucocorticoid exposure, NR3C1 methylation, circadian profiles, and clinical outcomes is required to define this regulatory interface (Figure 2).

4.3 | Cellular Clocks Gate Demethylation Capacity and Generate Locus-Specific Rhythmic Demethylation Units

Cellular clocks are autonomous circadian oscillators driven by the CLOCK/BMAL1–PER/CRY transcription–TTFL, generating intrinsic temporal organization independent of systemic rhythms [121, 122]. Beyond controlling clock gene expression, cellular clocks regulate transcriptional programs, chromatin states, and stress responses, thereby shaping cellular adaptability [123–126].

Rhythmic DNAm remodeling represents an important layer of circadian regulation. Clock components can modulate active demethylation pathways involving TET enzymes and 5-hydroxymethylcytosine (5hmC), creating temporal windows for regulatory DNA demethylation [28, 125, 127]. Bmal1 regulates stress-associated epigenetic responses through Tet3 and 5hmC dynamics, while circadian demethylation of specific CpG regions cooperates with rhythmic enhancers to regulate clock-controlled transcription [28, 125].

In OC, the TET2–5hmC axis may be remodeled during therapeutic stress and resistance evolution, contributing to adaptive transcriptional states [128–130]. Serum cfDNA 5hmC profiling also shows potential for predicting chemotherapy resistance in HGSOC [130]. Thus, clock–DNAm coupling may influence OC progression and treatment response, requiring validation through time-resolved epigenomics, single-cell analyses, and functional studies (Figure 2).

5 | Circadian Clock Genes and Their Methylation Patterns as Biomarkers

5.1 | Core Clock Gene-Specific Hypermethylation as an Early Warning Signal

OC, particularly HGSOC, remains highly lethal due to the lack of sufficiently sensitive and specific early detection strategies [1]. CA125 has limited performance in early-stage disease and may be elevated in benign conditions, highlighting the need for additional molecular biomarkers [1]. DNAm alterations have emerged as promising molecular indicators because of their stability, detectability, and compatibility with liquid biopsy approaches using ctDNA and cfDNA [15].

Within the circadian–OC regulatory axis, methylation-mediated silencing of core clock genes represents a potential biomarker source. Yeh et al. [27] showed that ARNTL (BMAL1) promoter methylation occurs in a subset of OC cells and is associated with repressive chromatin states, reduced expression, impaired cisplatin sensitivity, and altered c-MYC rhythmicity. ctDNA/cfDNA methylation profiling shows early detection potential in OC, with marker selection and pre-analytics affecting performance; multimarker strategies may improve accuracy [15, 131].

However, bulk methylation profiles may be confounded by tumor purity and cellular heterogeneity. Single-cell multi-omics studies in HGSOC have revealed distinct methylation patterns among tumor lineages, indicating that bulk analyses may overlook rare subpopulations with metastatic potential [132]. Clinical application further requires standardized methylation thresholds, as ARNTL/BMAL1 hypermethylation varies according to CpG sites, sample type, detection platform, tumor DNA fraction, and analytical methods [133]. For cfDNA/ctDNA panels, integrated scoring models and standardized pre-analytical procedures may be required.

Therefore, circadian-related methylation loci should currently be considered complementary candidate markers rather than independent biomarkers. Their diagnostic value requires validation across early-stage OC, high-risk populations, and diverse subtypes, with assessment beyond CA125 and established methylation panels [15, 131]. (Table 1).

5.2 | Rhythmic Epigenomic Features and Prognostic Stratification

HGSOC exhibits substantial clinical heterogeneity, with patients of similar FIGO stages and treatment regimens showing

different recurrence risks and survival outcomes, indicating that conventional parameters cannot fully reflect tumor intrinsic states [145]. DNAm-based epigenomic patterns provide stable stratification features, and integration with circadian activity and immune characteristics may add a temporal dimension to prognostic classification.

Global methylation profiles have prognostic relevance in HGSOC. Lo Riso et al. [139] developed the OriPrint DNAm-based cell-of-origin classifier and identified fallopian tube epithelial-like and ovarian surface epithelial-like subgroups, with the latter associated with more aggressive phenotypes and poorer outcomes. Zhao et al. [140] identified circadian-related genes linked to prognosis and immune features using TCGA OC data, while Xing et al. [141] showed that TIMELESS promotes OC progression and correlates with macrophage infiltration. However, methylation-based prognostic interpretation remains context-dependent. Wang et al. [134] identified four HGSOC methylation subtypes with distinct outcomes, emphasizing the importance of broader epigenomic backgrounds. Therefore, circadian-related methylation features should serve as complementary components of integrated prognostic models.

Therefore, circadian-related methylation features should be incorporated into integrated prognostic models with standardized validation and adjustment for clinical factors, BRCA/HRD status, tumor purity, and sampling time [134–137].

Overall, circadian-related methylation features represent complementary prognostic dimensions that require further validation to determine their incremental value beyond established clinical and molecular models. (Table 1).

5.3 | Epigenetic Consolidation of Clock Genes for Dynamic Monitoring of Platinum Resistance

Platinum-based chemotherapy combined with taxanes remains the standard first-line treatment for HGSOC; however, most patients eventually relapse and develop platinum resistance after initial responses [4, 138]. Resistance reflects continuous clonal evolution under therapeutic pressure, making early detection of resistant states before radiographic or CA125 changes clinically important [3, 5]. ctDNA enables serial monitoring of heterogeneous tumor-derived genetic and epigenetic alterations and has shown potential for assessing treatment response and detecting progression earlier than conventional approaches in some settings [3, 142, 143]. Longitudinal TP53-mutant ctDNA dynamics and personalized ctDNA strategies further support its utility, although interpretation requires consideration of tumor burden, lesion distribution, and treatment-induced cell death [144].

Circadian dysregulation may contribute to resistance evolution when stabilized by epigenetic remodeling. Wang et al. [82] demonstrated that PER2 loss in cisplatin-resistant OC models activates PI3K/AKT signaling, promotes EMT-like changes, suppresses apoptosis, and enhances drug efflux, with reduced PER2 expression accompanied by promoter CpG methylation, suggesting a potential resistance-associated marker. Evidence from SKOV3 models remains insufficient to confirm whether PER2 methylation reliably reflects resistant clone emergence in HGSOC plasma. Other clock regulators, including CLOCK, have also been linked to reduced cisplatin sensitivity through regulation of cell-cycle and stress-response pathways [146]. However, whether these methylation alterations directly drive resistance or reflect treatment-selected states remains unclear [32].

Future longitudinal studies integrating clock-related methylation, ctDNA alterations, and clinical parameters are required to determine their predictive value for resistance evolution and treatment adaptation. (Table 1).

6 | Therapeutic Implications: From Epigenetic Reprogramming to Chronotherapy-Based Precision Treatment

6.1 | Epigenetic Reprogramming as a Sensitization Hub

Platinum resistance is frequently associated with reversible epigenetic reprogramming, including abnormal DNAm and repressive chromatin remodeling, which stabilize resistance-related transcriptional states involving stress adaptation, apoptosis, immune regulation, and differentiation [147, 148]. Thus, the therapeutic value of epigenetic resetting lies in reversing these constraints and restoring drug sensitivity through DNA demethylation or chromatin relaxation [6, 149].

In OC, DNA demethylating agents have emerged as potential sensitizers. A randomized Phase II trial showed that guadecitabine combined with carboplatin could support the strategy of epigenetic priming followed by platinum rechallenge in platinum-resistant recurrent OC [150], with earlier studies demonstrating feasibility [151]. Moreover, combinations of guadecitabine or azacitidine with immune checkpoint inhibitors suggest that epigenetic modulation can reshape the tumor microenvironment and enhance anti-tumor immunity [149, 152]. HDAC inhibition with vorinostat has also shown potential for improving chemotherapy synergy [153]. Collectively, epigenetic resetting represents a promising strategy to overcome resistance-associated states and optimize combination therapies in OC (Table 2).

6.2 | Chronotherapy as Time-Dimensioned Precision Treatment

Therapeutic responses in OC may be influenced not only by drug selection and dosage but also by host circadian states. Chronotherapy incorporates treatment timing into therapeutic strategies by exploiting circadian variations in drug metabolism, tissue tolerance, hematopoiesis, and DNA damage repair to optimize efficacy and reduce toxicity [154–156].

Early clinical studies suggested potential treatment-time effects in OC. Hrushesky et al. [157] reported that morning

TABLE 1 | Potential clinical applications, analytical considerations, and current limitations of circadian-related DNA methylation biomarkers in ovarian cancer.

Biomarker or molecular feature	Potential application	Evidence and principal findings	Heterogeneity and analytical considerations	Threshold or scoring strategy	Evidence level and key limitations	References
ARNTL/BMAL1 promoter methylation	Early detection; molecular stratification; platinum-response prediction	Detected in a subset of OC cells and associated with ARNTL silencing, altered c-MYC rhythms, and cisplatin response	Varies by subtype, CpG site, tumor purity, sample type, and assay platform; bulk analysis may mask minor subclones	No universal cutoff; locus- and assay-specific thresholds or composite scores are needed	Preclinical evidence; limited clinical and early-stage validation; added value beyond CA125 is unknown	[27, 133]
PER2 promoter methylation	Platinum-resistance monitoring; response stratification characteristics and outcomes; circadian signatures are associated with prognosis and immune features.	Associated with reduced PER2, PI3K/AKT activation, EMT, apoptosis inhibition, and drug efflux in resistant OC models	Mainly based on SKOV3 models; applicability across HGSOC and tissue–plasma concordance remain unclear	No validated resistance cutoff; change from pretreatment baseline may be more informative	Preclinical evidence; requires longitudinal plasma validation; causal relevance remains uncertain	[32, 82]
Global or regional HGSOC methylation subtypes	Prognostic stratification; recurrence-risk assessment	Methylation-defined subgroups show different survival, residual disease, and molecular features	Influenced by tumor purity, stromal/immune admixture, cell of origin, platform, and clinical covariates	Based mainly on clustering, classifier probabilities, or multigene scores	Retrospective clinical evidence; requires prospective validation against FIGO stage, residual disease, and BRCA/HRD status	[134–138]
OriPrint cell-of-origin signature	Biological subclassification; prognosis	Distinguishes fallopian tube epithelial-like and ovarian surface epithelial-like HGSOC subgroups	Influenced by tumor purity, lineage admixture, reference cells, platform, and cohort composition	Classifier probability or composite score; no universal cutoff	Retrospective evidence; requires independent validation and assessment of added prognostic value	[139]
Circadian-related molecular signatures	Prognostic and immune stratification	Circadian gene signatures correlate with survival and immune characteristics	Derived mainly from bulk transcriptomes and affected by cellular composition, sampling time, and phase desynchronization	Cohort-specific risk scores; integrated methylation–expression models are needed	Retrospective bioinformatic evidence; indirect support for DNAm–clock coupling; no prospective validation	[140, 141]
cfDNA/ctDNA methylation panels incorporating circadian loci	Early detection; recurrence and resistance monitoring	Multilocus methylation panels may improve OC detection, especially when combined with mutations or protein markers	Affected by low tumor fraction, hematopoietic cfDNA, sample handling, bisulfite loss, and sequencing depth	Multilocus scores are preferable; cutoffs should be trained and independently validated	Early translational evidence; circadian loci remain unvalidated; stage-specific performance and comparison with CA125 are needed	[15, 131]

(Continues)

TABLE 1 | (Continued)

Biomarker or molecular feature	Potential application	Evidence and principal findings	Heterogeneity and analytical considerations	Threshold or scoring strategy	Evidence level and key limitations	References
Longitudinal clock-related ctDNA methylation changes	Dynamic response and resistance monitoring	Serial ctDNA changes may precede imaging or CA125 progression in some settings	Changes may reflect tumor burden, DNA shedding, treatment effects, clonal selection, and sampling interval	Patient-specific baseline changes or minimal detectable change may be preferable	Early translational evidence; no validated clock-specific algorithm; prospective outcome correlation is needed	[3, 142–144]

Abbreviations: AKT, protein kinase B; ARNTL, aryl hydrocarbon receptor nuclear translocator-like; BMAL1, brain and muscle ARNT-like 1; BRCA, BReast CAncer susceptibility gene; CA125, cancer antigen 125; cfDNA, cell-free DNA; c-MYC, cellular MYC proto-oncogene; CpG, cytosine-phosphate-guanine; ctDNA, circulating tumor DNA; DNAm, DNA methylation; EMT, epithelial–mesenchymal transition; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; OC, ovarian cancer; PER2, period circadian regulator 2; PI3K, phosphoinositide 3-kinase; SKOV3, Sloan-Kettering ovarian cancer cell line 3.

Adriamycin followed by evening cisplatin administration improved tolerability in advanced OC, while Lévi et al. [158] demonstrated reduced hematological and renal toxicity with circadian scheduling of anthracycline/cisplatin therapy. However, these studies were limited by small sample sizes, outdated regimens, and lack of molecular stratification, with benefits mainly observed in toxicity reduction rather than tumor control.

Recent studies provide mechanistic support for OC chronotherapy. Romero-Franco et al. [159] demonstrated circadian regulation of DNA end resection and homologous recombination (HR) repair by CRY1, suggesting that temporal DNA repair capacity may influence responses to platinum agents and PARP inhibitors. Malhan et al. [22] further linked PARP inhibitor-associated circadian disruption with treatment toxicity, although causality remains unclear. Therefore, current evidence supports biological plausibility but not routine clinical application.

Future randomized trials should integrate treatment timing, molecular biomarkers, pharmacokinetic/pharmacodynamic parameters, and liquid biopsy monitoring to determine the clinical value of chronotherapy in precision OC management (Table 2).

6.3 | Therapeutic Time Windows and Efficacy Evidence of DNAm–Clock Coupling

In OC, the most clinically validated association between DNAm and therapeutic response involves the HR repair pathway. The KOMET study demonstrated that BRCA1 promoter methylation was associated with improved responses to PARP inhibitors and platinum chemotherapy, supporting its potential as a theragnostic biomarker [160]. Further analyses indicated that predictive accuracy depends on complete BRCA1 allele methylation status rather than binary methylation classification alone [161]. Importantly, HR-related methylation states are dynamic. Menghi et al. [162, 163] showed that chemotherapy-induced BRCA1 promoter demethylation restored BRCA1 expression and contributed to platinum resistance, while RAD51C promoter demethylation was associated with PARP inhibitor resistance.

The convergence between HR methylation and circadian regulation lies in their shared influence on DNA repair capacity. Romero-Franco et al. [159] demonstrated circadian oscillations of DNA end resection and HR repair regulated by CRY1, suggesting that temporal variation in repair activity may affect responses to platinum agents and PARP inhibitors. Consistently, diurnal BRCA1/BRCA2 expression patterns provide further support for integrating temporal regulation into HR-targeted therapies [165]. However, treatment-specific evolutionary trajectories should be considered, as RAD51C demethylation after niraparib resistance may restore PARP inhibitor resistance while preserving carboplatin sensitivity [164].

Therefore, future models should integrate HR methylation profiles, allele-specific status, ctDNA dynamics, clonal evolution, treatment pressure, and circadian variables to better define therapeutic windows. (Table 2).

TABLE 2 | Therapeutic implications of epigenetic reprogramming and chronotherapy in ovarian cancer.

Therapeutic strategy/ molecular target	Mechanistic rationale and key findings	Therapeutic implication	Current limitations and future directions	References
Epigenetic reprogramming with DNA demethylating agents	Abnormal DNA methylation contributes to platinum-resistant transcriptional states; guadecitabine-mediated DNA demethylation may restore platinum sensitivity and enhance response to platinum rechallenge	Epigenetic priming followed by chemotherapy may overcome resistant phenotypes in recurrent OC	Clinical benefit remains heterogeneous; optimal patient selection biomarkers and methylation-based response predictors require validation	[147–151]
DNA methylation modulation combined with immunotherapy	DNMT inhibition can reshape tumor immune microenvironment and enhance anti-tumor immune responses when combined with immune checkpoint blockade	Potential strategy to improve immunotherapy responsiveness in OC	Need identification of immune–epigenetic biomarkers and confirmation in larger clinical trials	[149, 152]
HDAC inhibition and chromatin remodeling strategies	HDAC inhibitors such as vorinostat can induce chromatin relaxation and enhance chemotherapy-induced tumor cell killing	Combination therapy approach for overcoming chemoresistance	Limited clinical evidence; optimal combinations, dosing schedules, and toxicity profiles remain unclear	[153]
Chronotherapy-based chemotherapy scheduling	Circadian rhythms influence drug metabolism, DNA repair, hematopoiesis, and normal tissue tolerance; timed chemotherapy may optimize efficacy and reduce toxicity	Potential approach for improving treatment tolerability and therapeutic index	Early studies mainly demonstrated toxicity reduction rather than improved tumor control; modern molecular stratification is lacking	[154–158]
Circadian regulation of DNA repair and platinum/ PARP inhibitor response	CRY1 regulates circadian oscillations of DNA end resection and homologous recombination repair, suggesting time-dependent variation in DNA repair capacity	Provides mechanistic basis for treatment-time optimization of platinum agents and PARP inhibitors	Clinical relevance of repair oscillations remains unconfirmed; requires integration with pharmacokinetics, pharmacodynamics, and molecular biomarkers	[159]
BRCA1 promoter methylation as a theragnostic biomarker	BRCA1 promoter methylation is associated with homologous recombination deficiency and improved sensitivity to platinum chemotherapy and PARP inhibitors; complete allele-specific methylation status provides greater predictive accuracy	Potential biomarker for selecting patients likely to benefit from HR-targeted therapies	Binary methylation classification may be insufficient; allele-specific methylation assessment and standardized detection methods are needed	[160, 161]

(Continues)

TABLE 2 | (Continued)

Therapeutic strategy/ molecular target	Mechanistic rationale and key findings	Therapeutic implication	Current limitations and future directions	References
Dynamic HR pathway methylation monitoring during treatment evolution	Chemotherapy-induced BRCA1 demethylation can restore BRCA1 expression and promote platinum resistance; RAD51C demethylation contributes to PARP inhibitor resistance	Longitudinal methylation monitoring may predict acquired resistance and guide treatment adaptation	Requires integration of ctDNA, clonal evolution, treatment pressure, and temporal sampling strategies	[162–164]
Integration of circadian regulation with HR methylation status	Circadian control of HR activity and diurnal BRCA1/BRCA2 expression patterns suggest that DNA repair methylation states may interact with temporal regulation	Conceptual framework for defining therapeutic windows in platinum- and PARP inhibitor-based therapies	Direct evidence linking clock-controlled methylation states with treatment timing is currently insufficient	[159, 165]

Abbreviations: BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; CRY1, cryptochrome circadian regulator 1; DNMT, DNA methyltransferase; HDAC, histone deacetylase; HR, homologous recombination; HRD, homologous recombination deficiency; KOMET, the Korea PARP inhibitor biomarker study; PARP, poly(ADP-ribose) polymerase; PD, pharmacodynamic; PK, pharmacokinetic; RAD51C, RAD51 paralog C.

7 | Conclusions and Perspectives

The initiation, progression, and therapeutic resistance of OC arise from dynamic interactions among tumor states, microenvironmental pressures, treatment selection, and temporal regulation rather than isolated genetic events [11, 163, 166]. DNAm, as a stable yet plastic epigenetic layer, reflects tumor evolution and regulates circadian outputs through promoters, E-box elements, enhancers, and chromatin organization [14, 124, 167]. Conversely, circadian networks influence therapeutic responses by modulating DNA repair, metabolism, cell-cycle progression, immunity, and drug tolerance [22, 140]. Thus, DNAm–circadian integration provides a temporal framework for understanding OC adaptation. Mechanistically, promoter CpG hypermethylation may silence core clock genes, while methylation remodeling at E-box motifs and enhancers can alter CLOCK binding, chromatin accessibility, and transcriptional programs [27, 87, 168, 169]. Meanwhile, circadian signals such as melatonin, glucocorticoids, TET/5hmC pathways, and enhancer-associated demethylation can reshape methylation landscapes [111, 170–172], supporting a bidirectional regulatory network. Circadian-related methylation signatures may offer complementary value for early detection, prognosis, resistance monitoring, and therapy optimization. However, markers such as ARNTL/BMAL1 methylation remain exploratory, and their clinical utility requires validation beyond current CA125 and methylation-based panels [15–17, 27]. Integrating HR methylation profiles, ctDNA dynamics, and circadian variables may improve prediction of PARP inhibitor and platinum responses [165].

Future studies should combine time-resolved multi-omics, single-cell/spatial epigenomics, functional validation, and chronotherapy trials. Overall, DNAm–circadian coupling represents a context-dependent regulatory framework that may enable dynamic monitoring and precision therapy in OC.

Author Contributions

Min Xing: writing – original draft, resources. **Chang Zhou:** resources, writing – review and editing. **Yi Tang:** writing – review and editing. **Shuhui Xu:** writing – review and editing. **Shasha Zhou:** writing – review and editing. **Weiai Liu:** writing – review and editing. **Huiping Liu:** conceptualization, supervision, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

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