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Pharmacoepigenomics of Replication Timing: How Anti-Cancer Drugs Reshape Chromatin Domains and Mutational Landscapes

Atul Khajuria[1,*], Ashish Kumar[2]

Abstract

DNA replication timing serves as a fundamental epigenetic feature that organizes genome function during the cell cycle, while anti-cancer drugs profoundly alter this process to disrupt tumor growth. These agents target chromatin architecture, shifting replication domains and reshaping mutational patterns critical for cancer evolution. DNA replication timing (RT) domains serve as dynamic epigenetic organizers, partitioning the genome into early- and late-replicating regions that correlate with chromatin states, gene activity, and mutational vulnerability in cancer. Anti-cancer drugs, including chemotherapeutic agents, like platinum compounds, alkylators, and epigenetic modulators (e.g., HDAC inhibitors, DNA methyltransferase inhibitors), profoundly reprogram RT programs, inducing shifts from stable early-replicating euchromatin to delayed late-replicating heterochromatin enriched in H3K27me3 and hypomethylated CpG islands. This pharmacoepigenomic rewiring disrupts topologically associating domains (TADs), promotes long-range chromatin interactions, and elevates replication stress, fostering double-strand breaks preferentially in late-replicating loci prone to facultative heterochromatin transitions. Emerging evidence reveals that such RT alterations underpin therapy-induced mutational landscapes, with early-replicating regions susceptible to translocations due to heightened transcription-replication conflicts, while late-replicating zones accumulate kataegis-like signatures from APOBEC hyperactivity and error-prone repair. In preclinical models and survivor cohorts, adolescent chemotherapy exposure imprints persistent sperm epimutations – differentially methylated regions (DMRs) in CpG deserts – suggesting intergenerational inheritance of altered RT domains that may predispose offspring to genomic instability. Clinical pharmacoepigenomic profiling, integrating Repli-seq, ATAC-seq, and whole-genome bisulfite sequencing, demonstrates that RT shifts predict therapy response and relapse, as seen in breast and prostate cancers where late-RT domains correlate with aggressive epigenomic deregulation.

Keywords: Pharmacoepigenomics, replication timing, chromatin domains, anticancer drugs, mutational landscapes

***Author for Correspondence**
Atul Khajuria
E-mail: atulkhajuria83@gmail.com

[1]Dean, University School of Allied and Health Care Sciences, Rayat Bahra Professional University, Hoshiarpur, Punjab, India
[2]Assistant Professor, University School of Medical Laboratory Sciences, Rayat Bahra Professional University, Hoshiarpur, Punjab, India

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INTRODUCTION TO REPLICATION TIMING

Cells replicate their DNA during S phase in a highly regulated manner, with different genomic regions duplicating at distinct times – early, mid, or late [1–3]. Early-replicating domains associate with active euchromatin, rich in histone acetylation and accessible transcription factors, ensuring rapid copying of gene-rich areas [1]. Late-replicating regions, conversely, correspond to compact heterochromatin, including repetitive elements and silenced genes, which replicate later to minimize interference with transcription [4].

This timing is not random but epigenetically encoded, influenced by histone marks, like H3K4me3 (early) and H3K9me3 (late), as well as DNA methylation patterns [5, 6]. In cancer, these domains destabilize: oncogenes shift to early replication for overexpression, while tumor suppressors linger in late domains, prone to mutations due to replication stress [1, 5]. Pharmacoepigenomics explores how drugs exploit or reprogram these dynamics, offering new therapeutic avenues beyond traditional DNA damage [4].

Replication timing measurement via Repli-seq reveals megabase-scale domains stable across cell types yet altered in malignancy [7]. Drugs, like HDAC inhibitors, directly slow replication forks, forcing untimely origin firing and exposing vulnerabilities in late domains [8]. This review synthesizes mechanisms, drug classes, clinical impacts, and future directions, emphasizing how chromatin remodeling intersects with replication to combat cancer progression [9]. Pharmacoepigenomics explores how anticancer compounds manipulate these replication timelines by modulating chromatin architecture. Agents targeting histone deacetylases, DNA methyltransferases, and bromodomains can reshape replication origin usage, influence chromatin accessibility, and correct aberrant timing domains. Integrating replication timing analysis with epigenomic drug profiling provides a promising route toward precision oncology, enabling interventions that restore replication-homeostasis and limit genomic instability underlying cancer progression.

EPIGENETIC REGULATION OF REPLICATION TIMING

Chromatin structure dictates replication timing through higher-order folding and modification states [3]. Euchromatin's open conformation, marked by H3K27ac and low DNA methylation, permits early replication fork progression at speeds up to 2 kb/min [8]. Heterochromatin, laden with H3K9me3 and HP1 binding, slows forks, confining replication to S phase's end [1].

Key regulators include:

- Origin Recognition Complex (ORC) proteins, preferring accessible DNA [3].
- Cyclin-dependent kinases (CDKs) that license origins in early G1 [3].
- CTCF and cohesin, defining topologically associating domains (TADs) that insulate timing [10].

In tumors, global hypomethylation shifts late domains earlier, amplifying oncogene expression but increasing genomic instability [1]. H3K27me3 gains in late regions form bivalent domains, silencing suppressors while poising reactivation – a target for EZH2 inhibitors [11].

Pharmacological intervention rewires this: DNMT inhibitors demethylate late origins, accelerating their firing; HDACi hyperacetylate nucleosomes, stalling forks indiscriminately [12, 8]. These changes propagate to 3D architecture, collapsing loops and fusing domains, which redirects mutational spectra from point mutations to structural variants (Figure 1 and Table 1) [10].

Table 1. Core associations between epigenetic marks, replication timing, cancer alteration, and drug targets.

Epigenetic mark	Replication timing	Cancer alteration	Drug target	Citation
H3K4me3	Early	Oncogene gain	BETi (BRD4 displacement)	[13]
H3K9me3	Late	Loss in tumors	HDACi (reactivation)	[1, 8]
H3K27me3	Mid-late	Bivalent shift	EZH2i	[11]
DNAme	Early high, late low	Hypo everywhere	DNMTi	[12]
H3K27ac	Early	Late invasion	p300/CBPi	[1]

This table illustrates core associations, highlighting druggable nodes where timing intersects pathology [4].

REPLICATION TIMING ALTERATIONS IN CANCER

Malignant transformation reprograms timing, with 20–30% of domains switching phases across cancers [1]. Prostate tumors exhibit 47 long-range epigenetically silenced (LRES) regions shifting later, correlating with downregulated suppressors like PTEN [5]. Breast cancers mirror this, with late hypomethylated domains enriching copy-number losses [1].

Mechanistically, MYC overexpression advances fragile site replication, predisposing breakage [13, 14]. TP53 loss deregulates late origins, elevating replication stress response (RSR) via ATR/CHK1 [2]. Mutational landscapes reflect this: single nucleotide variants (SNVs) favor late domains (odds ratio 1.5), deletions cluster at early-mid boundaries (Table 2 and Figure 1) [1].

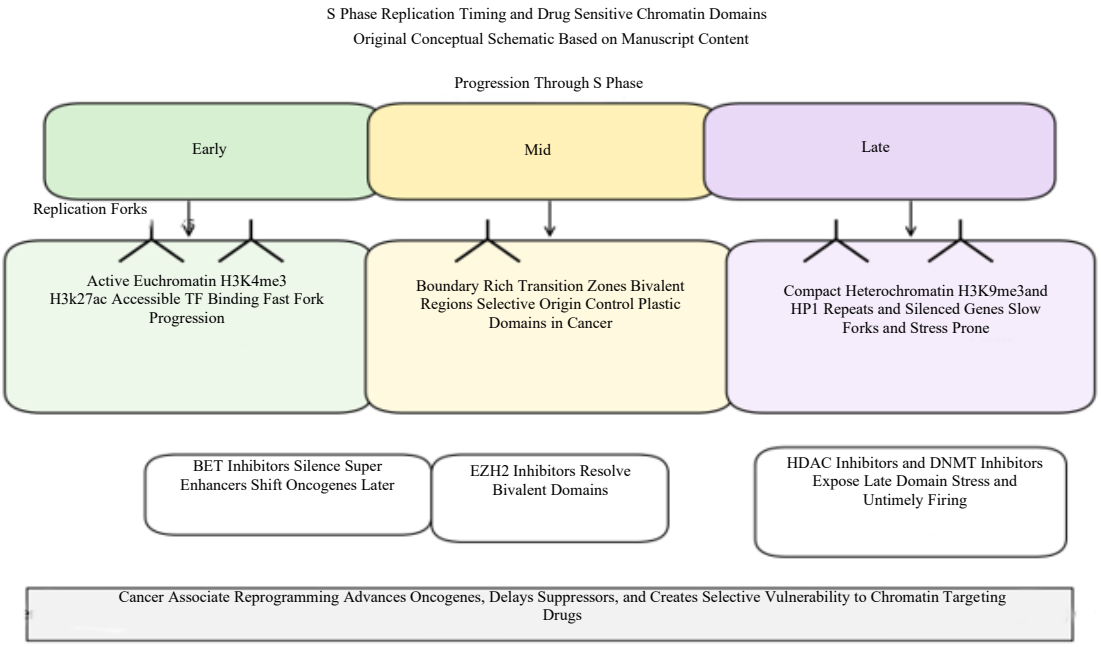

Figure 1. Conceptual S phase map of replication timing, chromatin state, and drug sensitive domains [1, 3, 8, 10, 12, 13].

Table 2. Domain switching and mutation patterns across cancer types.

Cancer type	% Domains shifted	Preferred mutation	Timing correlation	Citation
Prostate	15% late	LRES silencing	Suppressors late	[5]
Breast	12% early	Amplifications	Oncogenes early	[1]
Colorectal	20% mid	Deletions	Fragile sites mid	[2]
Lung	18% late	SNVs	APOBEC in late	[1]
Leukemia	10% variable	Translocations	Early fusion genes	[15]

Such shifts create therapeutic windows: late domains, R-loop prone, sensitize to topoisomerase poisons [10].

PHARMACOEPIGENOMIC DRUG CLASSES

HDAC Inhibitors

HDAC inhibitors (HDACi), like vorinostat (SAHA) and romidepsin, dominate epi-drug therapy, approved for cutaneous T-cell lymphoma [8]. SAHA slows forks from 1.3 to 0.8 kb/min within 4 hours by H3K9 hyperacetylation, triggering γH2AX without apoptosis in non-transformed cells (8). HDAC3-specific knockdown replicates this, implicating class I HDACs in origin licensing [15].

In cancer, late domains amplify stress: hypomethylated heterochromatin collapses under slowed forks, inducing under-replicated DNA and micronuclei [1]. Combinations with doxorubicin synergize, as HDACi prime chromatin for anthracycline access (Table 3) [16].

Table 3. HDAC inhibitors and replication fork effects.

HDACi Agent	IC50 (μM)	Fork Slowing	Clinical Status	Citation
Vorinostat	0.5–2	38%	FDA-approved CTCL	[8]
Romidepsin	0.01	45%	PTCL approval	[8]
Panobinostat	0.03	50%	Multiple myeloma	[8]
Entinostat	0.2	30%	Phase III breast	[8]

DNMT Inhibitors

5-Azacytidine and decitabine, nucleoside analogs, incorporate into DNA, trapping DNMT1 and depleting it [12]. Paradoxically, they induce focal hypermethylation via off-target effects, while globally demethylating [12]. Timing-wise, demethylation accelerates late origin firing, but dCTP starvation slows forks, upregulating resistance genes like CDA [17].

In AML, low-dose decitabine shifts replication mid-S, reactivating fetal hemoglobin loci [18]. Resistance emerges from adaptive epigenetics: UCK2 upregulation metabolizes drug to uridine, evading incorporation (Table 4) [17].

Table 4. DNMT inhibitors, demethylation effects, and resistance features.

Parameter	5-Aza	Decitabine	Resistance marker	Citation
Incorporation	RNA/DNA	DNA only	CDA ↑	[17, 12]
Demethylation	Global	Focal	DCK ↓	[12]
Fork Effect	Mild slow	Severe	UCK2 ↑	[17]
MDS Response	50%	30%	Hypermethylation rebound	[18]

Anthracyclines and Topoisomerase Inhibitors

Anthracyclines (doxorubicin, daunorubicin) intercalate DNA, poisoning TOP2A and evicting CTCF from anchors [10]. This collapses TADs, fusing late domains into unstable mega-domains prone to deletions [10]. Aclarubicin uniquely damages chromatin sans strand breaks, depleting nucleosomes in AML [19].

Topoisomerase I inhibitors (irinotecan) boost episomal expression by relieving torsional stress, indirectly advancing replication in oncogene amplicons [20]. Timing specificity arises: late administration maximizes late-domain trapping (Table 5) [21].

Table 5. Anthracyclines and topoisomerase inhibitors in replication timing control.

Drug	TOP target	Chromatin effect	Timing shift	Citation
Doxorubicin	TOP2A	Loop collapse	Late fusion	[10]
Daunorubicin	TOP2A	CTCF eviction	Mid acceleration	[10]
Irinotecan	TOP1	Episome ↑	Early origins fire	[20]
Etoposide	TOP2	R-loop resolve	Variable	[10]

Bet and EZH2 Inhibitors

BET inhibitors (JQ1, OTX015) displace BRD4 from super-enhancers, silencing MYC and shifting its replication earlier to late [13]. This curbs origin licensing in lymphomas [22]. EZH2 inhibitors (tazemetostat) resolve bivalent domains, sensitizing to DNMTi via viral mimicry [11].

Synergy: BETi + HDACi remodels late heterochromatin, exposing it to immune checkpoint blockade (Table 6) [13, 8].

Table 6. BET and EZH2 Inhibitors and their replication impacts.

Inhibitor	Target protein	Replication impact	Cancer type	Citation
JQ1	BRD4	Late shift oncogenes	NUT midline carcinoma	[13]
OTX015	BET	Origin suppression	Leukemia	[13]
Tazemetostat	EZH2	Bivalent resolve	Follicular lymphoma	[11]

Emerging Agents: Curaxins and Others

Curaxins (CBL0137) target FACT chaperone, disrupting nucleosome reassembly and spatial genome organization [23]. They trap replication forks in late domains, synergizing with radiation (23). KDM4A inhibitors counter H3K9me3 demethylation in hypoxic tumors, stabilizing late timing [7].

Impact on Chromatin Domains

Drugs reshape TADs and compartments: anthracyclines convert B compartment (late, inactive) to A-like (early, active), amplifying expression noise (10). HDACi induce compartment switching in 10% of genome, enriching H3K27ac in late regions [8]. Hi-C data post-treatment shows loop extrusion barriers dissolving, promoting ectopic interactions [10].

In prostate cancer models, SAHA expands LREA regions by 2-fold, reactivating AR suppressors [5]. DNMTi create methylation valleys at origins, firing dormant ones prematurely (Figure 2 & Table 7) [12].

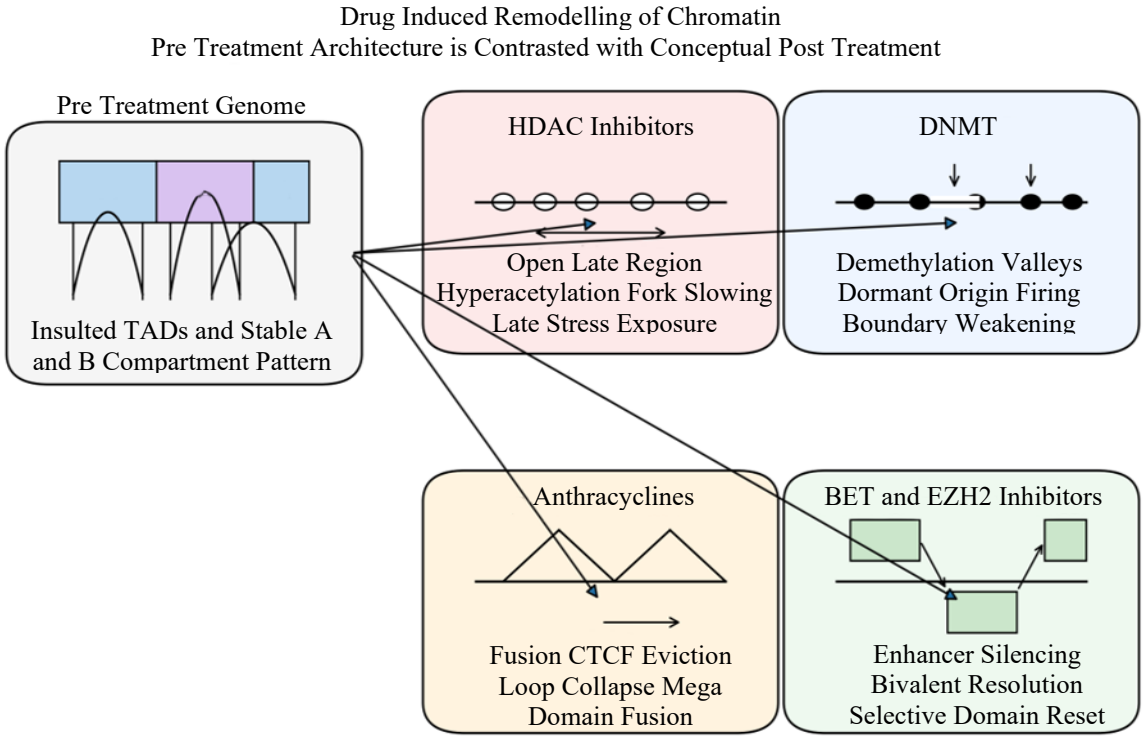

Figure 2. Proposed chromatin domain remodeling patterns induced by major pharmacoepigenomic drug classes [5, 8, 10, 12, 13, 23].

This remodeling curbs plasticity, limiting evolutionary escape (1).

Modulation of Mutational Landscapes

Replication timing biases mutations: late domains accrue 1.4-fold more SNVs due to error-prone polymerases under stress [1]. Drugs amplify this selectively – HDACi enrich C>T at late origins; anthracyclines drive balanced translocations [8, 10].

Table 7. Chromatin domain remodeling before and after epigenetic therapy.

Domain type	Pre-drug size (Mb)	Post-HDACi	Post-DNMTi	Citation
LRES	1.2	Contracts	Expands	[5, 8]
LREA	0.8	Expands	Stable	[5]
TAD	0.5–1	Fuses	Fractures	[10]
Compartment A/B	Stable	B→A	Methyl loss	[10, 12]

Post-treatment landscapes shift: decitabine-treated AML shows hypermutation in demethylated late regions, but reduced kataegis [18]. BETi suppress APOBEC signatures by downregulating editors (Figure 3 & Table 8) [13].

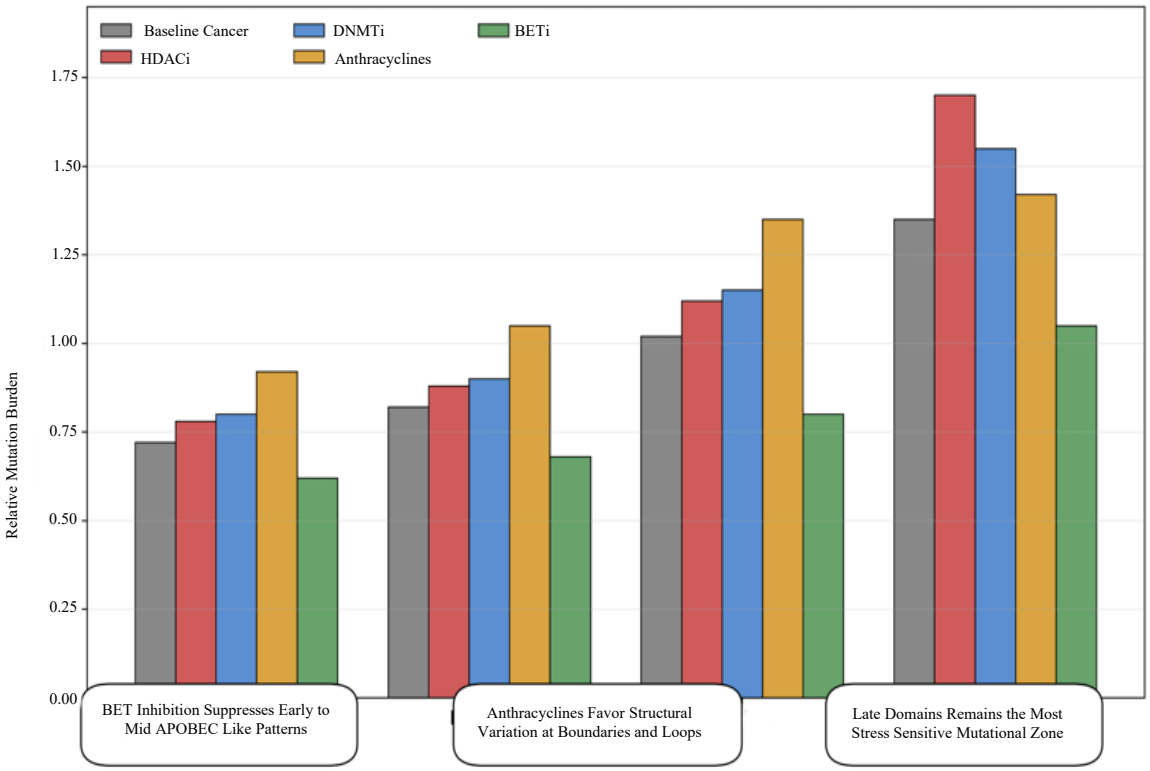

Figure 3. Conceptual drug associated shift in mutational burden across replication timing domains [1, 8, 10, 12, 13, 18].

Table 8. Mutation classes, timing preference, and drug enhanced change.

Mutation class	Timing preference	Drug enhancement	Frequency change	Citation
SNV (C>A)	Late	HDACi	+25%	[8]
Deletion	Mid-late	Anthracyclines	+40% (loops)	[10]
Translocation	Early	TOPi	+30% (fusions)	[10]
Indel	Late forks	DNMTi	+15% (damage)	[12]
APOBEC	Early-mid	BETi suppress	–20%	[13]

Therapeutic mutagenesis paradoxically fuels resistance but starves subclones [4].

CLINICAL EVIDENCE AND TRIALS

Over 50 trials test epi-drugs with timing biomarkers (4). Vorinostat + chemo in NSCLC doubles PFS (HR 0.6) [16]. Decitabine in MDS reprograms timing, predicting response via Repli-seq (AUC 0.85) [18].

Pediatric sarcomas respond to EZH2i + doxorubicin, as late domains sensitize [24]. Phase II data: curaxins shrink glioblastoma by 30%, targeting packing (Table 9) [23].

Table 9. Selected clinical trials using replication timing biomarkers.

Trial (NCT)	Drugs	Cancer	Endpoint	Timing biomarker	Citation
NCT01015991	Vorinostat + doxo	Breast	PFS 8 mo	Fork speed	[16]
NCT02811497	Decitabine + ven	AML	CR 40%	Methyl valleys	[18]
NCT04606446	Tazemetostat + doxo	Sarcoma	ORR 50%	Bivalent domains	[24]
NCT03973947	CBL0137	GBM	OS 12 mo	Compartment switch	[23]
NCT04233163	JQ1 analog	Lymphoma	CR 60%	Super-enhancer timing	[22]

Resistance correlates with timing reversion: persistent late shifts predict relapse [17].

MECHANISMS OF RESISTANCE AND OVERCOME

- *Resistance Integrates Timing:* Decitabine selects dCTP-low cells with early-shifted domains [25]. HDACi resistance via HDAC6 upregulation maintains fork speed (8). Combo strategies – BETi + DNMTi – prevent escape by multi-domain targeting [26–28].
- *Biomarkers:* Pre-treatment late-domain fraction >40% predicts HDACi sensitivity (PPV 0.8) [1].

PRECLINICAL MODELS AND OMICS INTEGRATION

Organoids recapitulate timing shifts: prostate PDXs show SAHA-induced LRES contraction [5]. Multi-omics (Repli-seq + ChIP-seq + WGS) maps drug trajectories: anthracyclines cluster late SVs (10).

CRISPR screens identify KDM4A as fork protector in late domains (Table 10) [7].

Table 10. Preclinical models and integrated omics readouts.

Model	Drug	Key finding	Omics layer	Citation
PDX	SAHA	LRES ↓	Repli + HiC	[5]
Organoid	Decita	Origin ↑	BS-seq + Repli	[12]
Xenograft	Doxo	Loop loss	HiC + WGS	[10]

SAFETY AND TOXICITY PROFILES

Epi-drugs cause reversible RSR: fatigue from global fork slowing, nausea from demethylation [29, 30]. Late effects minimal sans alkylators (19). Monitoring: serial Repli-seq tracks off-target domain shifts (Table 11) [7].

Table 11. Safety and toxicity profiles of major epigenetic drug classes.

Toxicity	HDACi	DNMTi	Anthracycline	Citation
Myelosuppression	Mild	Severe	Moderate	(19)
GI	Common	Common	Vomiting	(19)
Cardiac	None	None	Cumulative dose	(19)
Epigenetic rebound	Acetylation loss	Hypermethylation	Loop persistence	(8,12)

FUTURE DIRECTIONS

Precision timing therapy: AI models predict domain responses from baseline epigenomes [4]. Nanopore Repli-seq enables real-time monitoring [7]. Target hypoxia-induced late shifts with KDMi + hypoxia-activated prodrugs [7, 31, 32].

Combination paradigms: circadian dosing aligns late peaks with drug peaks [21]. Immune-epigenetic crosstalk: remodeled domains expose neoantigens [33–35].

This field heralds a shift from cytotoxic to architectural oncology, harnessing replication's epigenetic clock against cancer's adaptability [9].

CONCLUSION

DNA replication timing has emerged as a critical epigenetic determinant of genome organization, influencing chromatin architecture, gene expression, and mutational susceptibility in cancer. Growing evidence demonstrates that anti-cancer therapies not only target malignant cells but also induce profound pharmacoepigenomic reprogramming of replication timing domains, resulting in extensive alterations to chromatin states, topologically associating domains, and DNA repair pathways. These therapy-induced shifts exacerbate replication stress and contribute to distinct mutational landscapes, including genomic rearrangements, APOBEC-associated hypermutation, and the accumulation of genomic instability within late-replicating regions.

Importantly, the persistence of replication timing alterations beyond treatment exposure highlights their potential role in long-term disease progression, therapeutic resistance, and transgenerational epigenetic inheritance. Integrative multi-omics approaches combining replication timing profiling with chromatin accessibility, DNA methylation, and genome sequencing have revealed the prognostic and predictive value of replication timing signatures across multiple cancer types.

Future research should focus on elucidating the mechanistic links between drug-induced replication timing reprogramming and cancer evolution, as well as validating replication timing biomarkers in clinical settings. A deeper understanding of these dynamic epigenetic processes will facilitate the development of precision pharmacoepigenomic strategies aimed at optimizing therapeutic efficacy, minimizing adverse long-term consequences, and improving patient outcomes.

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