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Review Article

Environmental Epigenetics: How External Factors Shape the Epigenome and Influence Disease Risk

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Abstract

The human epigenome serves as a molecular interface between genome and environment, dynamically orchestrating gene expression without altering DNA sequence. Over the past decade, high-resolution epigenomic technologies and large-scale cohort studies have established that external exposures, including air pollutants, dietary patterns, endocrine-disrupting chemicals, psychological stressors, and early-life adversity, induce lasting, sometimes transgenerational, alterations in DNA methylation, histone post-translational modifications, and non-coding RNA profiles. These environmentally driven epigenetic changes underpin a spectrum of non-communicable diseases, including cancer, cardiovascular disease, metabolic syndrome, and neuropsychiatric disorders. Critically, the reversibility of epigenetic marks has catalysed a new class of pharmacological agents, epidrugs, several of which hold regulatory approval, with an expanding pipeline targeting BET bromodomains, EZH2, and locus-specific methylation via CRISPR-dCas9 fusions. Epigenetic clocks and circulating cell-free DNA methylation signatures are emerging as powerful translational biomarkers for biological ageing, cancer screening, and disease prognostication. This review synthesises current mechanistic understanding, catalogues evidence linking environmental exposures to epigenome perturbation, and charts a roadmap toward precision epigenetic medicine, where pharmacological, lifestyle, and gene-editing interventions are tailored to individual exposome histories.

Keywords: Environmental epigenetics, DNA methylation, histone modifications, non-coding RNA, transgenerational inheritance, disease susceptibility, personalized medicine.

1. Introduction

The central dogma of molecular biology, as originally conceived, implied a largely immutable information flow from genome to phenotype. Environmental epigenetics fundamentally challenges this paradigm. The epigenome, comprising DNA methylation, histone modifications, chromatin remodelling complexes, and non-coding RNAs,

constitutes a dynamic regulatory layer that continuously integrates environmental signals and translates them into stable alterations in gene expression programs.[1] Unlike somatic mutations, most epigenetic modifications are enzymatically reversible, rendering them both biological sensors of environmental injury and compelling pharmacological targets.

The scope of environmental inputs that modulate the epigenome is vast: ambient air pollution, dietary macronutrient and micronutrient composition, toxic chemical exposures, physical activity, sleep architecture, psychosocial adversity, and the gut microbiome collectively constitute what epidemiologists term the 'exposome'. [2] Epidemiological and mechanistic studies confirm that exposure-induced epigenetic dysregulation occurs across the life course, from preconception and in utero programming through senescence, and may persist across generations via germline epigenetic inheritance. [3]

The pharmaceutical relevance is equally profound. DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors have transformed oncology, while second-generation epidrugs targeting EZH2, BRD4, and KDM6A broaden the therapeutic landscape. [4] Furthermore, CRISPR-dCas9 epigenome editing platforms now allow locus-specific methylation or acetylation with unprecedented precision, opening avenues for therapeutic gene reactivation without permanent genome modification. [5]

This review, structured for readers in pharmaceutical sciences, (i) delineates the major epigenetic mechanisms and their environmental determinants; (ii) synthesises evidence linking specific exposures to disease-associated epigenome perturbations; (iii) evaluates current and emerging epidrugs; (iv) presents cutting-edge technologies enabling epigenomic interrogation; and (v) outlines future directions toward precision epigenetic medicine.

2. Major Epigenetic Mechanisms and Environmental Sensitivity

2.1 DNA Methylation

DNA methylation at cytosine residues within CpG dinucleotides is the most extensively characterised epigenetic mark. In mammals, it is catalysed by DNMT3A and DNMT3B (de novo methylation) and maintained by DNMT1 during replication. Active demethylation proceeds through TET enzyme-mediated oxidation to 5-hydroxymethylcytosine (5hmC) and subsequent base-excision repair. [6] Aberrant methylation, hypermethylation of tumour suppressor promoters or global LINE-1 hypomethylation, represents a near-universal feature of human cancers and is inducible by multiple environmental stressors. For example, tobacco smoke

exposure robustly induces hypomethylation at AHRR (cg05575921), a locus now used clinically to infer smoking history from blood DNA. [7]

2.2 Histone Modifications

Histones undergo more than 60 distinct post-translational modifications, acetylation, methylation, phosphorylation, and ubiquitination, collectively constituting the 'histone code.' Histone acetyltransferases (HATs) promote transcriptional activation by relaxing chromatin compaction, whereas HDAC-mediated deacetylation restores repression. Heavy metal exposures, particularly arsenic and cadmium, remodel histone landscapes at critical metabolic and inflammatory gene loci, contributing to cardiometabolic disease. [8] Psychosocial stress elevates glucocorticoid signalling, altering H3K4me3 and H3K27me3 patterns at glucocorticoid-responsive genes, with enduring effects on hypothalamic-pituitary-adrenal (HPA) axis reactivity. [9]

2.3 Non-Coding RNA

MicroRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) modulate gene expression post-transcriptionally and interact reciprocally with DNA methylation and histone modification machinery. Environmental endocrine disruptors, including bisphenol A (BPA) and phthalates, dysregulate miRNA expression in reproductive and metabolic tissues. [10] Circulating exosomal miRNAs (miR-21, miR-155) respond rapidly to particulate matter exposure and are emerging as non-invasive cardiovascular disease biomarkers. [11]

2.4 Chromatin Remodelling and 3D Genome Architecture

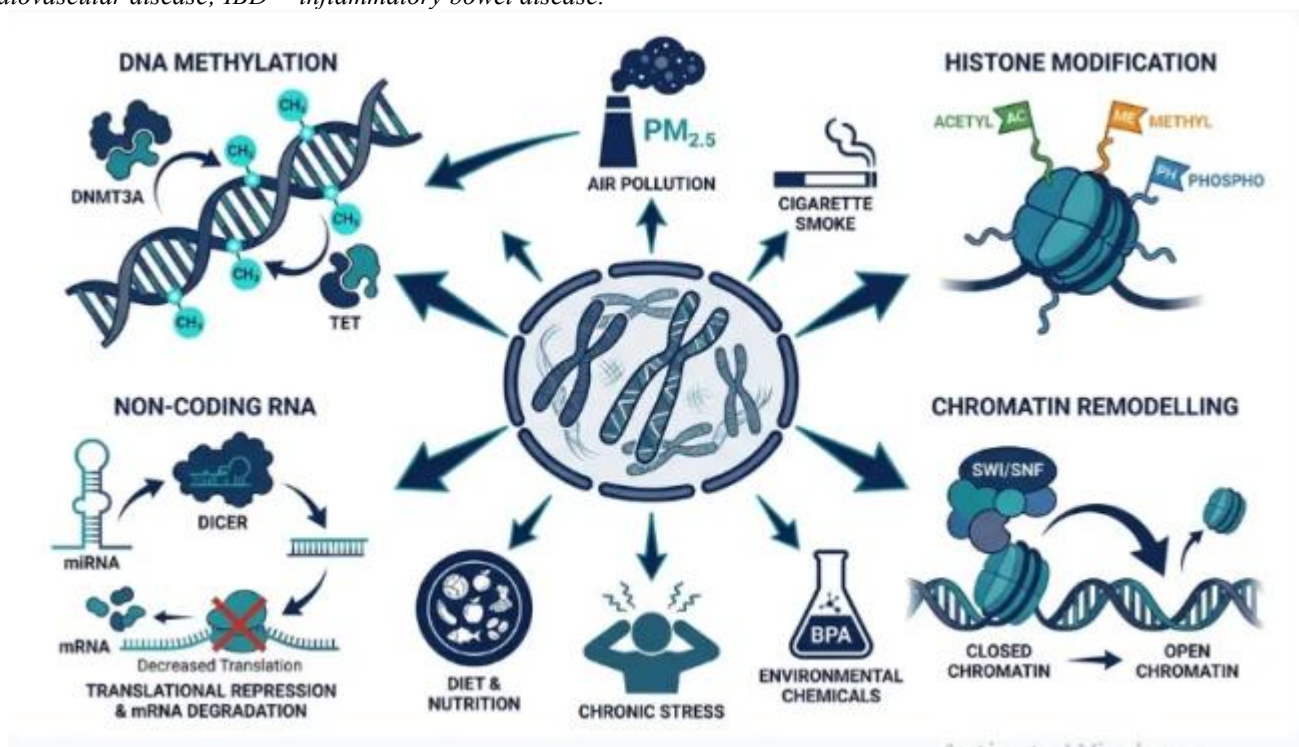
ATP-dependent chromatin remodelling complexes (SWI/SNF, NuRD, INO80) and cohesin/CTCF-mediated topologically associating domains (TADs) regulate gene accessibility in three-dimensional nuclear space. Environmental hypoxia disrupts cohesin loading at CTCF boundary elements, collapsing TAD insulation and enabling aberrant enhancer-promoter interactions. [12] Table 1 summarises the key mechanisms, actors, environmental triggers, and associated diseases.

Table 1. Principal Epigenetic Mechanisms, Environmental Triggers, and Associated Diseases

Epigenetic Mechanism	Key Molecular Actors	Environmental Triggers	Target Genes/Pathways	Disease Association
DNA Methylation (5mC)	DNMT1, DNMT3A/B, TET1-3	Air pollution, diet, tobacco	CDKN2A, MLH1, LINE-1	Cancer, neurodegeneration
Histone Acetylation (H3K27ac)	HATs (p300/CBP), HDACs	Heavy metals, stress hormones	NF-κB, inflammatory cytokines	CVD, metabolic syndrome
Histone Methylation (H3K4me3)	KMT2A/MLL, KDM5 family	Psychosocial stress, alcohol	HOX genes, development	Psychiatric disorders
Non-coding RNA (miRNA, lncRNA)	Dicer, Drosha, Argonaute	Endocrine disruptors, UV	mRNA stability, chromatin	Autoimmune, endocrine disorders
Chromatin Remodelling (SWI/SNF)	ARID1A, SMARCA4, BRD4	Ionising radiation, hypoxia	DNA repair, p53 network	Lung cancer, IBD

HAT = histone acetyltransferase; *HDAC* = histone deacetylase; *KMT* = lysine methyltransferase; *CVD* = cardiovascular disease; *IBD* = inflammatory bowel disease.

Source: Data compiled from reference [12]


Figure 1. Schematic of environmental epigenetic mechanisms and molecular machinery.

Caption: Create A detailed scientific infographic. At the centre: a cell nucleus with chromosome. Four branching panels: (1) DNA methylation - double helix with CH₃ groups at CpG sites, DNMT3A and TET enzymes as molecular structures; (2) Histone modification- nucleosome with acetyl (green), methyl (orange), phospho (blue) flags; (3) Non-coding RNA-miRNA hairpin processed by Dicer, post-

transcriptional silencing arrows; (4) Chromatin remodelling-SWI/SNF complex repositioning nucleosome. Environmental icons surrounding nucleus: factory (PM_{2.5}), cigarette, chemical flask (BPA), stressed figure, food plate.

Sources: Authors illustration adapted from references [1,6]

2. Environmental Determinants of Epigenome Perturbation

2.1 Air Pollution and Particulate Matter

Fine particulate matter (PM_{2.5}) is perhaps the most globally significant environmental epigenetic stressor. Large-scale epigenome-wide association studies (EWAS) conducted in European and North American cohorts have identified PM_{2.5}-associated methylation changes at NOTCH4, HIF3A, and inflammatory gene loci, with effect sizes that partially mediate PM_{2.5}-associated cardiovascular mortality.[13] Methylation changes at cg06126421 (IER3) have been associated with PM_{2.5} exposure in a dose-dependent fashion, persisting up to five years post-exposure cessation, underscoring the durability of pollutant-induced epigenetic marks.[14]

2.2 Dietary Exposures and Nutritional Epigenomics

The one-carbon metabolic pathway, supplying S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methyltransferases, is acutely sensitive to dietary folate, methionine, choline, and vitamin B12 status. Maternal periconceptional folate supplementation durably alters offspring methylation at imprinted loci, with implications for neural tube defect prevention and cancer susceptibility.[15] Conversely, high-sugar Western diets promote DNMT1 stability via mTORC1-mediated phosphorylation, promoting hypermethylation in adipose and pancreatic tissue and contributing to insulin resistance. [16]

2.3 Endocrine-Disrupting Chemicals

BPA and structurally related compounds bind oestrogen receptors (ER α/β) and recruit DNMT3B to the ESR1 promoter, silencing oestrogen receptor expression in breast epithelium, a mechanistic link to hormone-independent breast

cancer.[10] Transgenerational rodent studies demonstrate that developmental BPA exposure epigenetically programmes obesity phenotypes in F1-F3 generations, mediated through altered methylation at imprinted loci including Igf2 and H19.[17]

2.4 Psychosocial Stress and Early Life Adversity

Seminal work established that childhood abuse hypermethylates the NR3C1 exon 1F promoter in hippocampal tissue, reducing glucocorticoid receptor (GR) expression and impairing stress response modulation. [18] More recent multi-cohort EWAS in large population samples confirm that adverse childhood experiences (ACEs) are associated with accelerated epigenetic ageing as measured by GrimAge2, independent of adult lifestyle factors. [9] Critically, these stress-associated methylation signatures are detectable in peripheral blood and saliva, offering clinically accessible biomarkers.

2.5 Radiation and Genotoxic Stressors

Ionising radiation induces DNA strand breaks that trigger ATM/ATR kinase cascades, catalysing γ -H2AX formation, a histone phosphorylation mark at double-strand break sites serving both as a DNA damage signal and scaffold for repair complexes. Sublethal radiation exposure at occupationally relevant doses induces persistent DNMT3A downregulation, causing progressive CpG island shore hypomethylation in haematopoietic stem cells, potentially contributing to radiation-induced leukaemia risk. [19] Table 2 catalogues key stressors, their epigenetic signatures, and clinical biomarkers, while Figure 2 presents the Heat-map of EWAS-derived differential methylation signatures across five major environmental exposures.

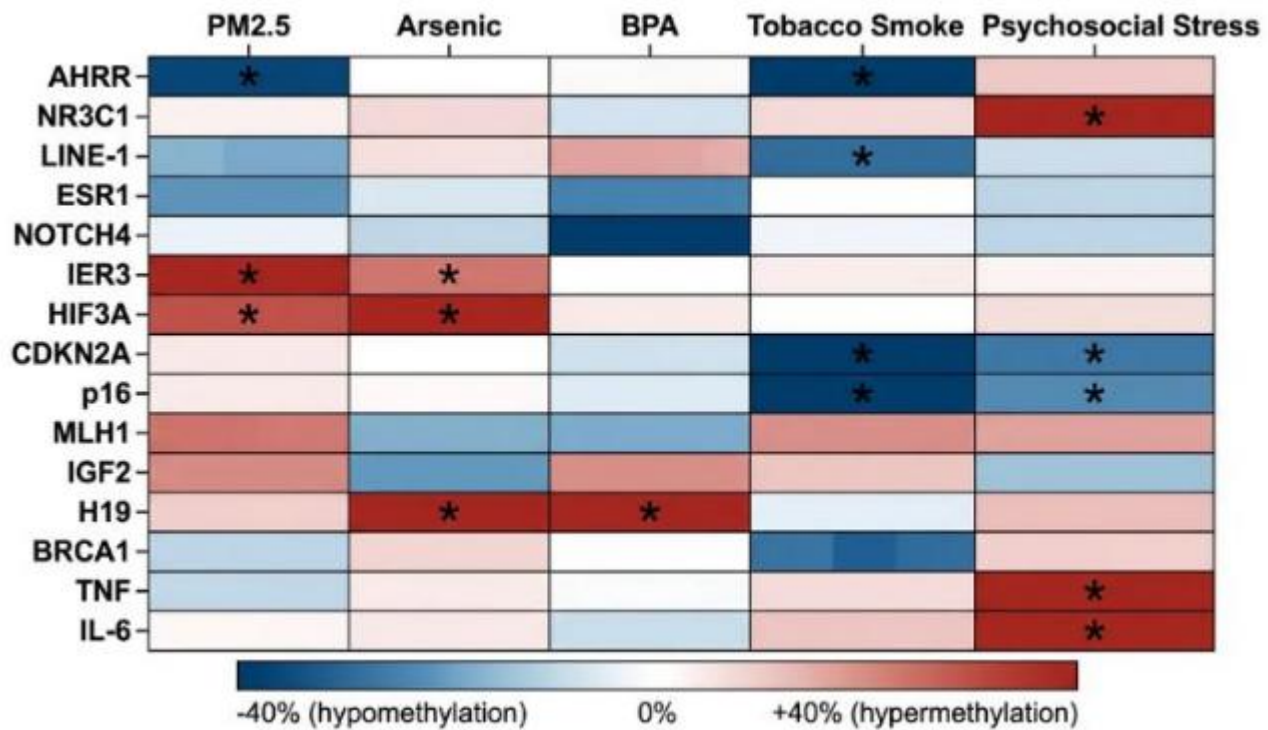
Table 2. Environmental Stressors, Their Epigenetic Signatures, and Clinical Biomarkers

Environmental Stressor	Exposure Route	Epigenetic Change	Biomarker	Clinical Relevance
Fine Particulate Matter (PM2.5)	Inhalation / transplacental	LINE-1 hypomethylation; NF-κB activation	Blood 5mC level	Cardiovascular mortality
Arsenic (iAs)	Drinking water, food	Global hypomethylation, p16 silencing	Urinary 8-OHdG	Bladder/lung carcinoma
Bisphenol A (BPA)	Food packaging, plastics	ESR1 promoter methylation	Cord blood methylome	Breast cancer, obesity
Tobacco Smoke (ETS)	Inhalation / secondhand	AHRR hypomethylation (cg05575921)	Saliva/blood DNA	COPD, lung cancer
Chronic Psychosocial Stress	HPA axis, glucocorticoids	NR3C1 (GR) promoter methylation	Hair cortisol levels	MDD, PTSD, metabolic disease

ETS = environmental tobacco smoke; COPD = chronic obstructive pulmonary disease; MDD = major depressive

disorder; HPA = hypothalamic-pituitary-adrenal; 8-OHdG = 8-hydroxy-2'-deoxyguanosine.

Source: Data from reference [19]

**Figure 2. Heat-map of EWAS-derived differential methylation signatures across five major environmental exposures.**

A bioinformatics-style heat-map. X-axis: five environmental exposures (PM2.5, Arsenic, BPA, Tobacco Smoke, Psychosocial Stress). Y-axis: 15 CpG loci labelled by gene name (AHRR, NR3C1, LINE-1, ESR1, NOTCH4, IER3, HIF3A, CDKN2A, p16, MLH1, IGF2,

H19, BRCA1, TNF, IL-6). Diverging colour scale: deep blue (hypomethylation -40%) → white (no change) → deep red (hypermethylation +40%). Significant cells marked with asterisks. Source adopted from [Refs: 13, 14].

3. Epigenome-Disease Nexus: From Mechanism to Pathology

3.1 Cancer

Epigenetic dysregulation is now recognised as a hallmark of cancer, frequently preceding somatic mutation accumulation.²⁰ Promoter hypermethylation of tumour suppressor genes (CDKN2A, MLH1, BRCA1) silences critical cell cycle checkpoints and DNA repair pathways, while global LINE-1 hypomethylation promotes chromosomal instability. Environmental carcinogens — tobacco-derived nitrosamines, arsenic, aflatoxin — are mechanistically linked to specific methylation signatures that stratify cancer risk independently of genetic factors.⁷ Cell-free DNA methylation patterns in plasma now enable multi-cancer early detection with sensitivities exceeding 70% at 99% specificity for several cancer types.²¹

3.2 Cardiovascular and Metabolic Disease

Epigenetic ageing acceleration, quantified by GrimAge2 or DunedinPACE, robustly predicts cardiovascular mortality beyond traditional Framingham risk factors.²² PM2.5-associated LINE-1 hypomethylation correlates inversely with endothelial nitric oxide synthase (eNOS) promoter methylation, linking pollution exposure to endothelial dysfunction. In type 2 diabetes, islet-specific CpG methylation at TCF7L2 and PPARGC1A correlates with insulin secretory failure and is inducible by dietary fat overload in human pancreatic islets.

3.3 Neuropsychiatric Disorders

Evidence from post-mortem brain methylome studies, twin studies, and imaging-epigenomics confirms that schizophrenia, major depressive disorder, and autism spectrum disorder are associated with convergent hypermethylation of GABAergic gene promoters (GAD1, RELN) and aberrant imprinting at 15q11-q13.⁹ Childhood adversity-induced oxytocin receptor gene (OXTR) promoter hypermethylation impairs social cognition, positioning the neuronal methylome as both a disease biomarker and therapeutic target.¹⁸

3.4 Transgenerational Epigenetic Inheritance

Perhaps the most transformative implication of environmental epigenetics is the transmission of environmentally-induced

epigenetic states across generations. Rodent models demonstrate that paternal stress, diet, and toxicant exposure alter sperm small RNA cargo and methylome, altering offspring metabolic and behavioural phenotypes.³ Human epidemiological data from famine cohorts provide indirect support, with grandchildren of famine-exposed individuals exhibiting altered metabolic risk profiles, suggesting epigenetically-mediated intergenerational programming that demands new frameworks in preventive medicine.

4. Pharmacological Modulation of the Epigenome: Epidrugs and Beyond

The reversibility of epigenetic modifications has driven intense drug discovery efforts. The epidrug landscape in 2025 encompasses DNMT inhibitors, HDAC inhibitors, HAT modulators, histone methyltransferase inhibitors, bromodomain inhibitors, and locus-specific epigenome editors.⁴

DNMT inhibitors 5-azacitidine and decitabine remain frontline therapies for myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). Their mechanism — irreversible covalent trapping of DNMT1 on hemimethylated DNA, leading to passive demethylation across cell divisions — reactivates silenced tumour suppressors but produces global hypomethylation, limiting the therapeutic window.⁴ EZH2 inhibitors (tazemetostat) block H3K27 trimethylation, restoring polycomb-silenced tumour suppressor expression in follicular lymphoma and epithelioid sarcoma.²³ BET bromodomain inhibitors prevent BRD4 from reading H3K27ac marks at super-enhancers driving oncogene expression in haematological and solid malignancies.

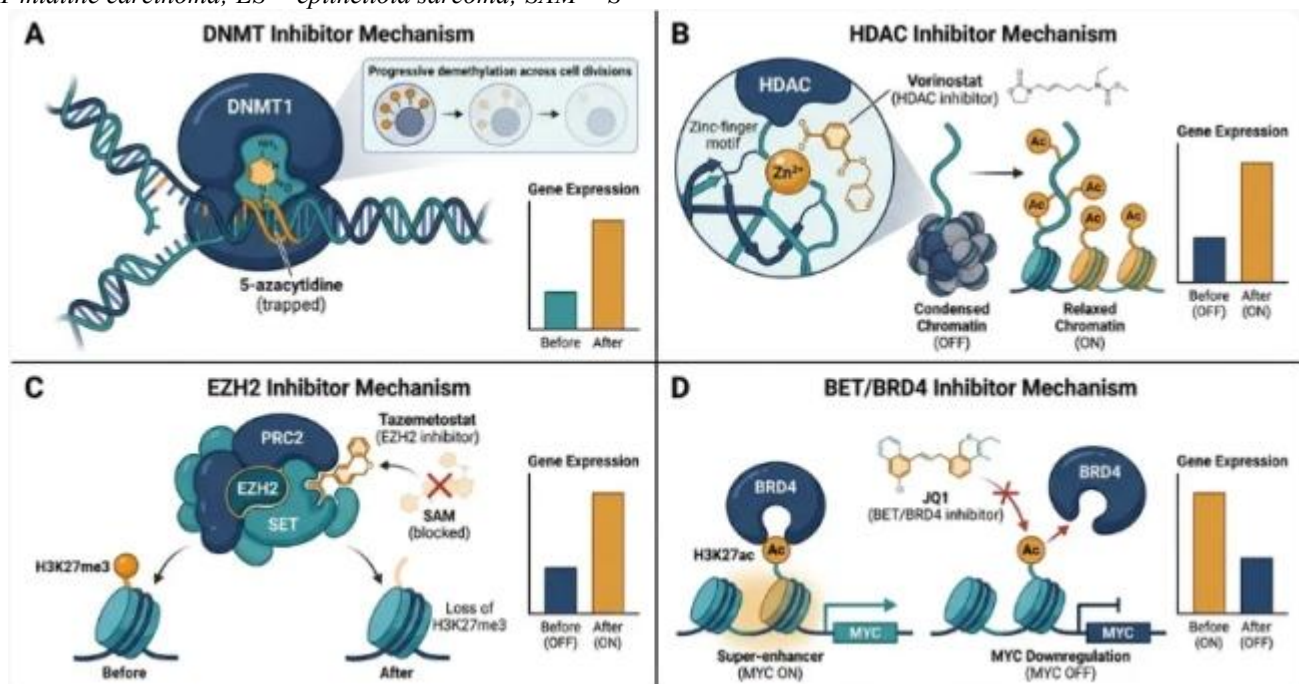
Dietary and nutraceutical epigenome modulators — sulforaphane (HDAC inhibitor from broccoli), resveratrol (SIRT1 activator), and folate (methyl donor) — provide lower-potency but broadly accessible interventions for disease prevention.¹⁵ The emerging frontier is CRISPR-dCas9-based epigenome editing: fusion of catalytically dead Cas9 to DNMT3A, TET1, p300 (HAT), or LSD1 (KDM1A) enables programmable, locus-specific epigenetic modification without double-strand DNA breaks, offering transformative potential for gene therapy of epigenetically silenced disorders.⁵ Table 3 summarises current and investigational epidrugs.

Table 3. Approved and Investigational Epidrugs: Mechanisms, Indications, and Epigenetic Targets

Drug / Intervention	Target Mechanism	FDA Status	Indication	Epigenetic Action
5-Azacitidine (Vidaza)	DNMT inhibition	Approved (2004)	MDS, AML	Global demethylation, reactivates silenced tumour suppressors
Decitabine (Dacogen)	Irreversible DNMT1 trapping	Approved (2006)	MDS, AML	DNA incorporation traps DNMT1; passive demethylation
Vorinostat (SAHA)	Pan-HDAC inhibition	Approved (2006)	CTCL	Hyperacetylation → chromatin opening, apoptosis induction
JQ1 / BET inhibitors	BRD4 bromodomain blockade	Phase II/III	NMC, TNBC, inflammation	Prevents BRD4 reading H3K27ac at super-enhancers
Tazemetostat (Tazverik)	EZH2 methyltransferase inhibition	Approved (2020)	Follicular lymphoma, ES	Reduces H3K27me ₃ ; restores tumour suppressor expression
Dietary Folate / SAM precursors	Methyl donor supplementation	Nutraceutical	Neural tube defects, CVD	Restores SAM pool → normalises DNA methylation patterns

MDS = myelodysplastic syndrome; AML = acute myeloid leukaemia; CTCL = cutaneous T-cell lymphoma; NMC = NUT midline carcinoma; ES = epithelioid sarcoma; SAM = S-

adenosylmethionine; SAHA = suberoylanilide hydroxamic acid.


Figure 3. Mechanism of action of approved epidrugs targeting DNMT, HDAC, EZH2, and BRD4.

Four-panel mechanistic diagram, pharmaceutical illustration style, teal-navy-amber palette, white background. Panel A: DNMT inhibitor — DNA replication fork showing DNMT1 covalently trapped by 5-

azacytidine incorporation; label progressive demethylation across cell divisions. Panel B: HDAC inhibitor — zinc-finger HDAC active site with vorinostat chelating zinc ion; histone tail becomes acetylated and chromatin relaxes. Panel C:

EZH2 inhibitor — PRC2 complex with EZH2 SET domain, tazemetostat blocking SAM cofactor binding, loss of H3K27me3. Panel D: BET/BRD4 inhibitor — BRD4 bromodomain reading H3K27ac at super-enhancer, JQ1 competitively displacing acetyl-lysine, MYC downregulation. Each panel includes before/after gene expression bars. Source adopted from References: (4, 23).

5. Cutting-Edge Technologies for Epigenomic Interrogation

The rapid maturation of epigenomic technologies has transformed environmental epigenetics from a hypothesis-generating field into one generating mechanistic, population-scale, and clinically actionable data. Whole-genome bisulphite sequencing (WGBS) at single-CpG resolution, the Illumina EPIC 850K array, ChIP-seq for histone marks, and ATAC-seq for chromatin accessibility are now being applied to large biobank-linked cohorts.²⁴

Single-cell multi-omic approaches — scRNA-seq combined with scATAC-seq — enable simultaneous profiling of transcriptome and chromatin accessibility in the same cell, resolving epigenetic heterogeneity within tissues previously treated as homogeneous.²⁴ Long-read sequencing platforms (Oxford Nanopore, PacBio) directly detect 5mC and 5hmC at native DNA without bisulphite conversion, preserving strand-specific information and resolving repetitive elements inaccessible to short-read methods.

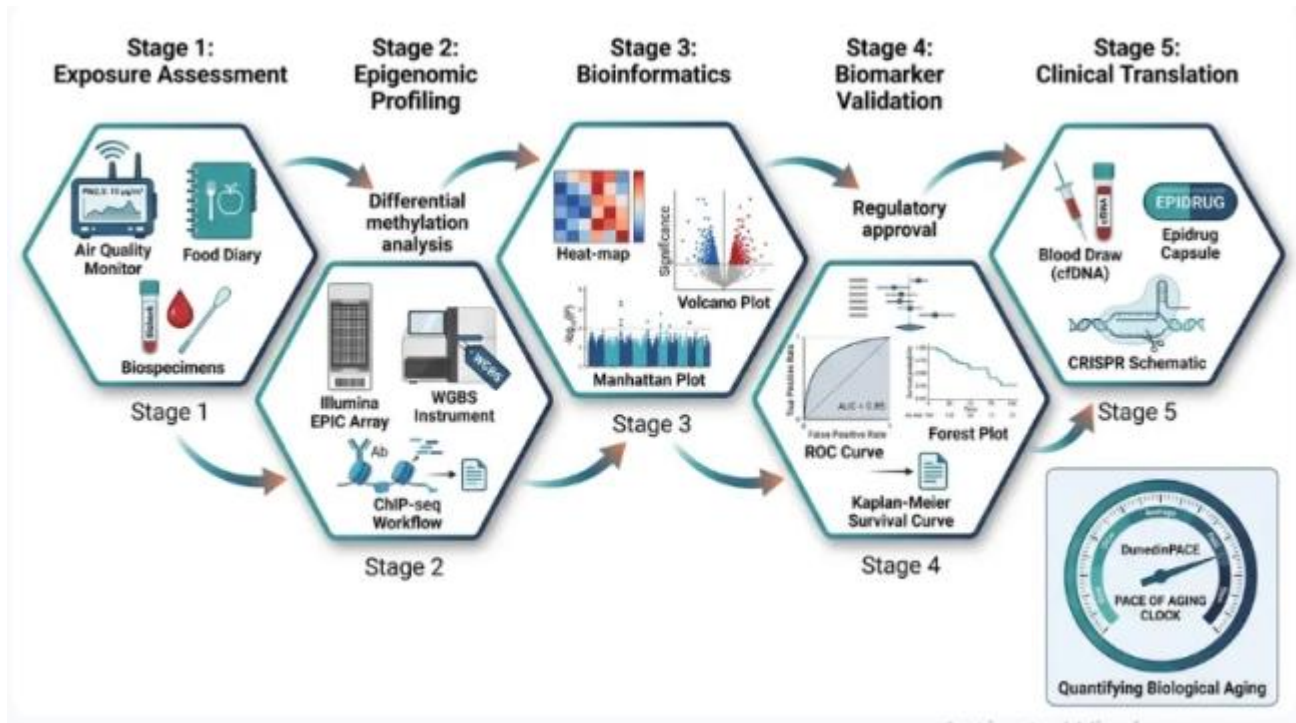
In the clinical translation domain, plasma cell-free DNA methylation profiling exploits tissue-of-origin methylation signatures to detect multiple cancer types from a single blood draw with high specificity.²¹ Epigenetic clock algorithms applied to peripheral blood methylome data generate quantitative biological age estimates that outperform chronological age in predicting mortality, morbidity, and treatment response.²² Table 4 summarises key technologies, their resolution, and translational applications.

Table 4. Technologies for Environmental Epigenomics: Capabilities, Resolution, and Translational Applications

Technology	Principle	Resolution	Clinical Utility	Key Limitations
WGBS	Bisulphite conversion + NGS	Single CpG, genome-wide	Discovery, biomarker atlases	High cost; large DNA input required
EPIC/850K Methylation Array	Bead-chip hybridisation	850,000 CpG sites	Epigenetic clocks, EWAS	Pre-selected CpGs; SNP interference
ChIP-seq	Chromatin immunoprecipitation + NGS	Histone mark, genome-wide	Enhancer mapping, drug targets	Requires fresh tissue; antibody variation
ATAC-seq / scATAC-seq	Tn5 transposase accessibility	Open chromatin regions	Single-cell accessibility profiling	Low-input protocols still maturing
CRISPR-dCas9 Epigenome Editing	Dead Cas9 fused to DNMT/TET/HAT	Locus-specific, programmable	Functional validation, gene therapy	Off-target effects; in vivo delivery challenges

WGBS = whole-genome bisulphite sequencing; NGS = next-generation sequencing; EWAS = epigenome-wide association

study; scATAC-seq = single-cell ATAC sequencing; cfDNA = cell-free DNA.



**Figure 4. Translational pipeline: from environmental epigenomic discovery to clinical biomarkers and therapeutics. **

Horizontal pipeline/flowchart, five interconnected hexagons, teal-to-navy gradient, white background. Stage 1 (Exposure Assessment): air quality monitor, food diary, biospecimen icons. Stage 2 (Epigenomic Profiling): EPIC array chip, WGBS instrument, ChIP-seq workflow. Stage 3 (Bioinformatics): heat-map, Manhattan plot, volcano plot. Stage 4 (Biomarker Validation): ROC curve, forest plot, Kaplan-Meier curve. Stage 5 (Clinical Translation): blood draw vial (cfDNA test), pill capsule (epidrug). Adopted from References [22, 24]

6. Epigenetic Clocks and Biomarkers: Translational Frontiers

Epigenetic clocks represent one of the most clinically consequential outputs of environmental epigenetics research. The Horvath clock, trained on 353 CpGs across 51 tissue types, accurately predicts chronological age and — when biological age exceeds chronological age (epigenetic age acceleration, EAA) — predicts mortality, cancer incidence, and age-related morbidity.²² The GrimAge2 clock, incorporating plasma protein methylation surrogates, achieves

superior mortality prediction compared to first-generation clocks, with PM2.5 exposure, poverty, and childhood adversity identified as leading drivers of EAA in population studies.⁹

DunedinPACE, derived from a longitudinal birth cohort, measures the pace of biological ageing rather than accumulated ageing, and is particularly sensitive to modifiable lifestyle and pharmaceutical interventions. Clinical trials of anti-ageing interventions increasingly use epigenetic pace-of-ageing as a primary or secondary endpoint, cementing its role as a surrogate outcome measure.²²

Beyond ageing, tissue-specific methylation biomarkers are entering clinical practice. SEPT9 methylation in plasma is cleared for colorectal cancer screening, while SHOX2/RASSF1A methylation in bronchoalveolar lavage improves lung cancer detection in indeterminate pulmonary nodules.²¹ The next frontier is multi-analyte cfDNA platforms combining methylation, fragmentomics, and copy-number variation for cancer-agnostic early detection. Table 5 summarises key clocks and circulating biomarkers.

Table 5. Epigenetic Clocks and Circulating Biomarkers: Environmental Determinants and Clinical Utility

Epigenetic Clock / Biomarker	Reference Population	Tissue Source	Environmental Accelerators	Translational Application
Horvath Clock (2013, updated 2022)	Multi-tissue pan-tissue	353 CpGs in blood/tissue	Smoking, obesity, alcohol	Biological age; cancer risk stratification
GrimAge2 Clock	Generation Scotland cohort	Whole blood methylome	Air pollution, poverty, ELS	Mortality prediction; clinical trial endpoint
DunedinPACE	Dunedin birth cohort (NZ)	Blood DNA methylome	ACEs, diet quality	Rate-of-ageing measure; geroscience interventions
cfDNA Methylation Signatures	Multi-cancer early detection	Plasma cell-free DNA	Occupational carcinogen exposure	Liquid biopsy; multi-cancer screening
miR-21 / miR-155 Panel	Inflammatory disease cohorts	Serum / exosomes	PM2.5, endocrine disruptors	CVD & autoimmune disease monitoring

ELS = early life stress; cfDNA = cell-free DNA; ACE = cardiovascular disease; EWAS = epigenome-wide association study; adverse childhood experience; NZ = New Zealand; CVD =

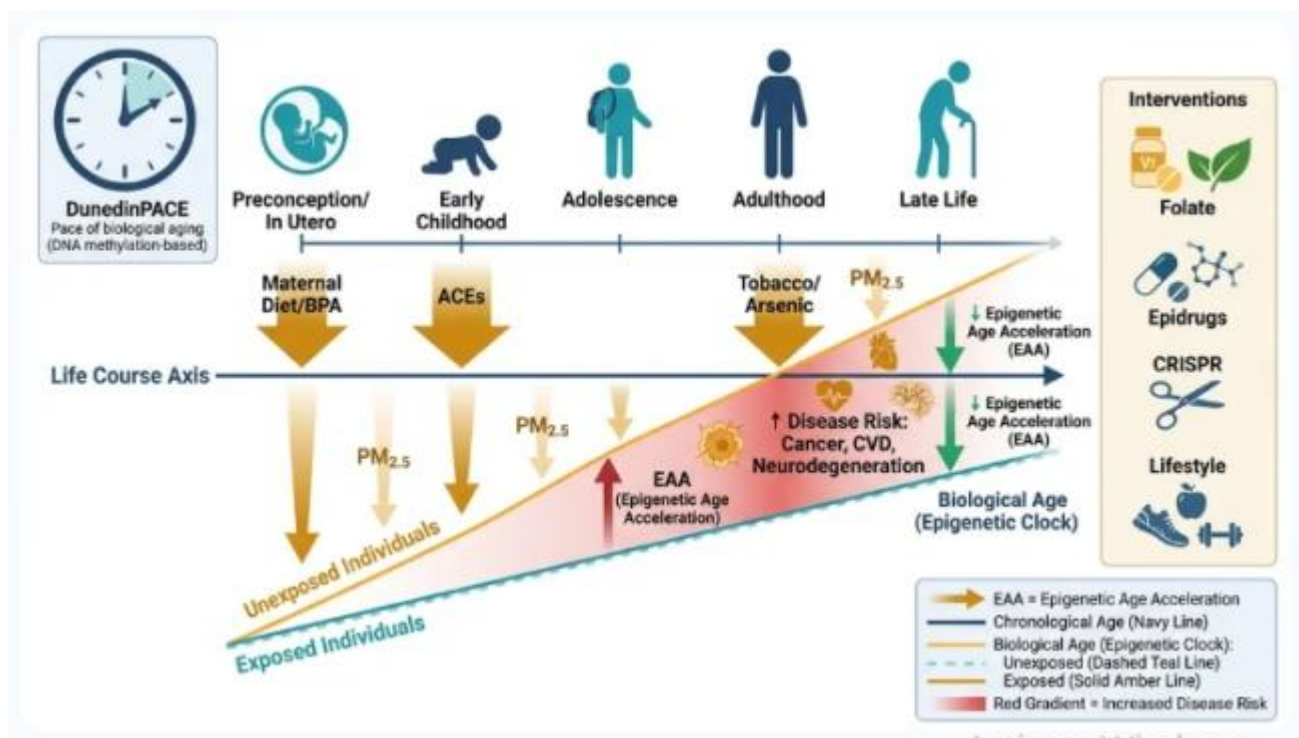


Figure 5. Epigenetic clock acceleration across the life course: environmental drivers and clinical consequences.

Sophisticated longitudinal timeline infographic, teal-navy-amber palette, white background. Central horizontal axis: human life course from Preconception/In Utero through Early Childhood, Adolescence, Adulthood, to Late Life. Above axis: smooth upward line labelled 'Chronological Age.' Below: second line

individuals curves above it (EAA). At key life stages, downward arrows labelled with stressors: maternal diet/BPA (preconception), ACEs (childhood), tobacco/arsenic (adulthood), PM2.5 (throughout). Gap between age lines shaded red proportional to disease risk (cancer, CVD, neurodegeneration labelled). Adopted from References (9, 22]

'Biological Age (Epigenetic Clock)' — in unexposed individuals tracks close to chronological, in exposed

7. Future Directions: Towards Precision Epigenetic Medicine

The convergence of multi-omic technologies, machine learning, and mechanistic epigenomics is enabling a paradigm shift from population-level epidemiology toward precision epigenetic medicine — interventions tailored to individual exposome trajectories and epigenome states.²⁵

Artificial intelligence-driven integration of methylome, transcriptome, proteome, and microbiome data is poised to generate composite epigenetic risk scores that outperform single-omic biomarkers in disease prediction. Federated learning frameworks, allowing multi-centre analysis without centralised data sharing, are being piloted for cross-cohort EWAS replication, addressing the perennial statistical power limitations of epigenetic association studies.²⁴

CRISPR-dCas9 epigenome editing has achieved proof-of-concept in imprinting disorders (Angelman syndrome), neurological diseases (ApoE modulation in Alzheimer's disease), and haemoglobinopathies (HbF reactivation via BCL11A silencing).⁵ As delivery vehicles mature — lipid nanoparticles for hepatic targets, adeno-associated virus for CNS — therapeutic epigenome editing will transition from bench to clinic, potentially offering single-treatment epigenetic corrections for conditions rooted in environmental programming.

Environmentally-adaptive pharmacogenomics represents another frontier: recognising that exposome-induced methylation changes at CYP450 and drug transporter gene promoters alter drug metabolism and pharmacokinetic parameters. Incorporating blood DNA methylation-based CYP2D6, CYP1A2, and SLCO1B1 activity surrogates into dosing algorithms could improve therapeutic outcomes and reduce adverse drug reactions.²⁵

Finally, the ethical and regulatory dimensions of environmental epigenetics demand urgent attention. Epigenetic biomarkers of environmental exposure risk exacerbating health inequity if used by insurers or employers. Regulatory frameworks for epidrugs must address their non-permanent yet potentially heritable epigenetic effects. Germline epigenome editing raises profound questions about intergenerational consent that bioethics frameworks are only beginning to address.

8. Conclusion

Environmental epigenetics has matured from a conceptual framework into a mechanistically-grounded, clinically actionable science. The accumulated evidence leaves no doubt: the epigenome is a dynamic, environmentally-responsive molecular archive of an individual's exposome, encoding disease risk across the life course and potentially across generations. The pharmaceutical sciences stand at the nexus of this revolution — both in developing epidrugs that

therapeutically reprogram disease-associated epigenomes and in utilising epigenetic biomarkers for precision diagnostics.

The next decade will witness the integration of epigenetic clock endpoints into Phase III clinical trials, the first regulatory approvals for CRISPR-dCas9 epigenome therapies, and routine incorporation of plasma cfDNA methylation profiling into oncological screening programmes. Realising this potential requires sustained investment in longitudinal cohort infrastructure, open-access multi-omic data platforms, and robust translational pipelines that carry mechanistic discoveries from bench to bedside — and ultimately to the populations whose health is most profoundly shaped by their environments.

Author Contributions

The author has significantly contributed to the study's conception, design, data collection, analysis, and interpretation. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accept full responsibility for the content and integrity of the work.

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Conflicts of Interest

The authors state that there are no financial, personal, or professional conflicts of interest associated with this research.

Ethical Approvals

This research did not involve the use of human participants or animal subjects and therefore did not require ethical clearance

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