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Part II: The Sound of Silence, Latent Iron Deficiency: Orchestrating Epigenetic Tunes of Neoplastic Transformation

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Abstract for Part II: The Sound of Silence, Latent Iron Deficiency Orchestrating Epigenetic Tunes of Neoplastic Transformation

Background: While chronic oxidative stress is an established driver of carcinogenesis, the mechanisms by which transient molecular insults are converted into stable, heritable pro-malignant states are a key area of investigation. Epigenetic modifications provide a plausible link between environmental or metabolic stressors and the long-term alterations in gene expression that precede overt cancer.

Objective: This review explores how chronic oxidative stress, often initiated by latent micronutrient deficiencies, orchestrates a durable epigenetic reprogramming that silences tumor-suppressor genes and activates oncogenic pathways. It details the transition from a reversible stress response to a fixed "epigenetic lock-in" that defines the premalignant state.

Findings: The manuscript details how persistent reactive oxygen species (ROS) disrupt the function of critical epigenetic-modifying enzymes, including iron-dependent TET and JmjC demethylases. This impairment leads to aberrant DNA hypermethylation at CpG islands and the deposition of repressive histone marks (e.g., H3K27me3), which silence key tumor-suppressor genes. Concurrently, non-coding RNAs (ncRNAs) guide these repressive complexes, reinforcing a malignant gene expression program that can be passed through cell divisions. This epigenetic memory explains the long latency periods observed in premalignant lesions and establishes a molecular foundation for field cancerization.

Conclusion: Epigenetic alterations function as the central mechanism translating chronic metabolic stress into a durable, cancer-prone cellular identity. These modifications are not only biomarkers for early risk assessment but also represent a crucial, druggable checkpoint. Therapeutic strategies targeting epigenetic regulators, such as DNMT, HDAC, and BET inhibitors, offer a promising avenue to reset the aberrant epigenetic landscape, thereby preventing or reversing malignant progression.

Introduction

Many patients have undetected biochemical stresses that cause chronic oxidative stress due to micronutrient deficiencies, inflammation, or environmental exposures. These stresses lead to the production of reactive oxygen species (ROS) that damage DNA, proteins, and lipids. DNA damage includes oxidized bases, missing bases, and strand breaks, with incomplete repair often causing mutations. Oxidative stress changes gene expression through chromatin and epigenetic modifications, suppressing protective genes and activating survival pathways, which can push cells toward malignancy. Iron deficiency, affecting nearly one of every four Americans despite normal hemoglobin levels,[1] weakens enzymes that remove repressive epigenetic marks, silencing genes crucial for differentiation, immunity, and metabolic stability, thereby promoting metabolic disruption and a pre-cancerous state.

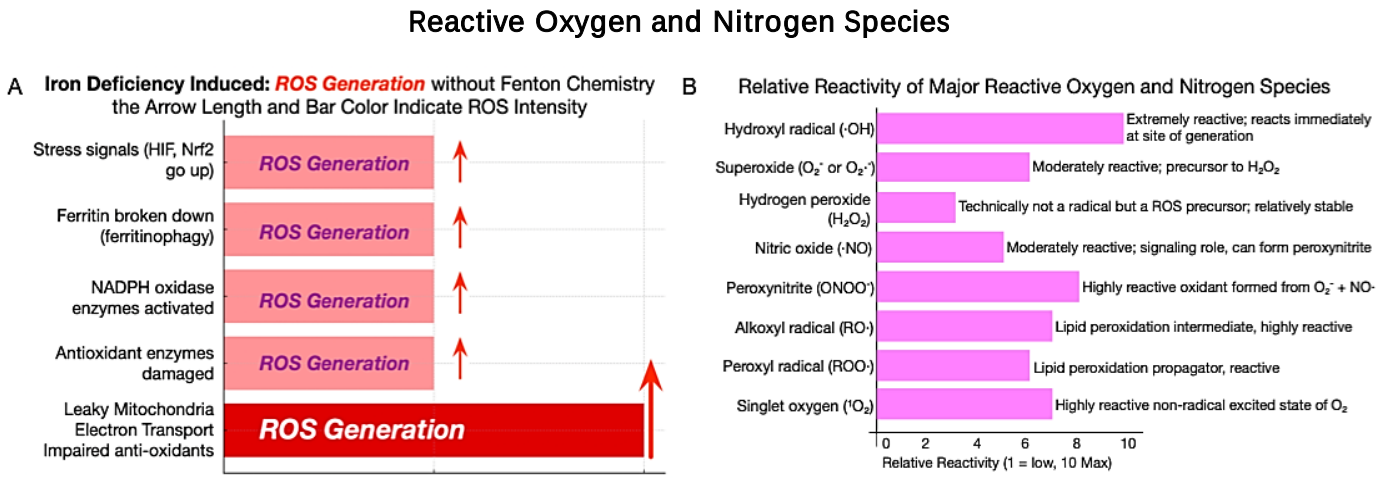

Figure 1 A, B *Legend*: ***Panel A:*** *Arrows and pink shading show each source's contribution to total ROS burden. The red base bar represents approximations of overall ROS under iron deficiency, plus metabolic pressures not tied to Fenton chemistry.*

Panel B: *Bar chart shows relative reactivity of ROS/RNS on a 1–10 scale (1 = low, 10 = high), based on chemical reactivity, not concentration. Highly reactive species (e.g., •OH, HOCl, $ONOO^-$) rank high; moderately reactive ones (e.g., H_2O_2) are mid-range; less reactive radicals (e.g., $O_2\bullet^-$, NO•) rank low. This shows why small changes in ROS generation or detoxification can amplify biologic effects when highly reactive species form.*

Abbreviations: *ROS, reactive oxygen species; RNS, reactive nitrogen species; HIF, hypoxia-inducible factor; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NOX, NADPH oxidase; ETC, electron transport chain.*

Reactive oxygen species (ROS) as the common pathway linking lifestyle exposures to epigenetic and metabolic dysregulation.

Multiple everyday exposures may converge to sustain a persistent ROS excess that damages DNA and imprints epigenetic changes, thereby lowering the threshold for potential malignant transformation.

Shortened and Simplified Oxidative Stress and Reactive Oxygen and Nitrogen Species as Harbingers of Carcinogenesis

Hidden biochemical changes precede tumors. Chronic oxidative stress from micronutrient deficiencies, inflammation, or environmental exposures disrupts normal physiology. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) from mitochondria, immune responses, or environmental insults damage DNA, proteins, and lipids, altering metabolism and immunity.[2]

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Three key transcription factor pathways are involved: NF-κB, chronically activated by oxidative stress, regulates inflammation and immune genes; HIF-1α and HIF-2α,[3] stabilized in hypoxia or iron deficiency, promote glycolysis and angiogenesis; and Nrf2,[4] which activates antioxidant genes but can support tumor survival.

These factors form a network driving inflammation, metabolism, and survival, contributing to cancer. Persistent stressors like iron deficiency, obesity, smoking, or chronic inflammation (Figure 3) cause error-prone DNA repair, leading to mutations.[5] Epigenetic marks on DNA and histones "lock in" maladaptive gene expression.[6,7,8] HIFs, Nrf2, and NF-κB amplify each other, reinforcing a cancer-prone metabolic state that persists even if stressors subside.[9,10,11,12]

Epigenetic Mechanisms of Malignant Transformation

The first part of this series of three manuscripts emphasized how oxidative stress, if unresolved, disrupts normal cellular adaptation. This manuscript represents the next step in understanding how these disturbances become ingrained in the cell's long-term memory through epigenetic mechanisms, such as DNA methylation and histone tail modification (Figures 2, 6, 7).

Epigenetic Regulation of Chromatin Architecture and Gene Expression (Repressed vs Active)

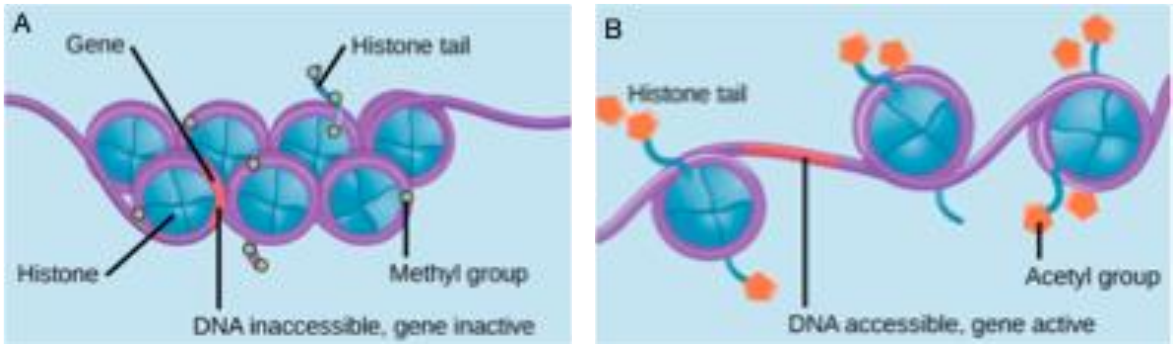

Figure 2 *Legend: Epigenetic marks, including DNA methylation and histone tail modifications, regulate whether chromatin is compacted and transcriptionally repressed (Panel A) or relaxed and transcriptionally active (Panel B).[13,14] Histone tail modifications act as molecular switches that control the accessibility of tumor-suppressor and oncogenic pathways. In healthy cells, these marks are dynamic, responding to physiologic cues such as oxygen availability, nutrient status, and redox balance.[15] During acute oxidative stress, such modifications are protective and reversible, enabling short-term survival. However, under chronic stress, epigenetic states may become fixed ("locked in") and heritable, establishing long-term gene-regulatory programs that predispose to malignant transformation and, in some cases, can be transmitted across generations.[16,17] Epigenetics thus refers to chemical modifications, including DNA methylation and histone modifications, that regulate gene activity without altering the underlying DNA sequence.*

Epigenetic marks like DNA methylation and histone modifications act as switches, opening or compacting chromatin.[18] In healthy cells, these marks adapt to oxygen, nutrients, and redox balance,[19] reversing under acute oxidative stress.[20] Chronic stress reduces plasticity: repressive methylation accumulates in malignant tissue and adjacent normal epithelium (field involvement), silencing tumor-suppressor genes while oncogenic programs remain accessible (Figure 2).[21] This shifts transient signaling to heritable regulation, persisting through cell divisions.

Oxidative stress creates a lasting epigenetic record, lowering the malignancy threshold over time. Clinically: (1) epigenetic changes precede visible dysplasia, altering gene expression in microscopically normal cells;[20,21] (2) these reversible marks are diagnostic and therapeutic targets via diet or drugs;[22] (3) micronutrient deficiencies, like iron, impair Fe^{2+}/α-ketoglutarate-dependent demethylases (TET and Jumonji-C), causing persistent methylation and tumor-suppressor silencing.[23] Chronic oxidative imbalance reprograms the genome. Aberrant marks

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are copied through cell divisions, perpetuating malignancy even after stress resolves, explaining why silent deficiencies and inflammation precede cancer by years.[24]

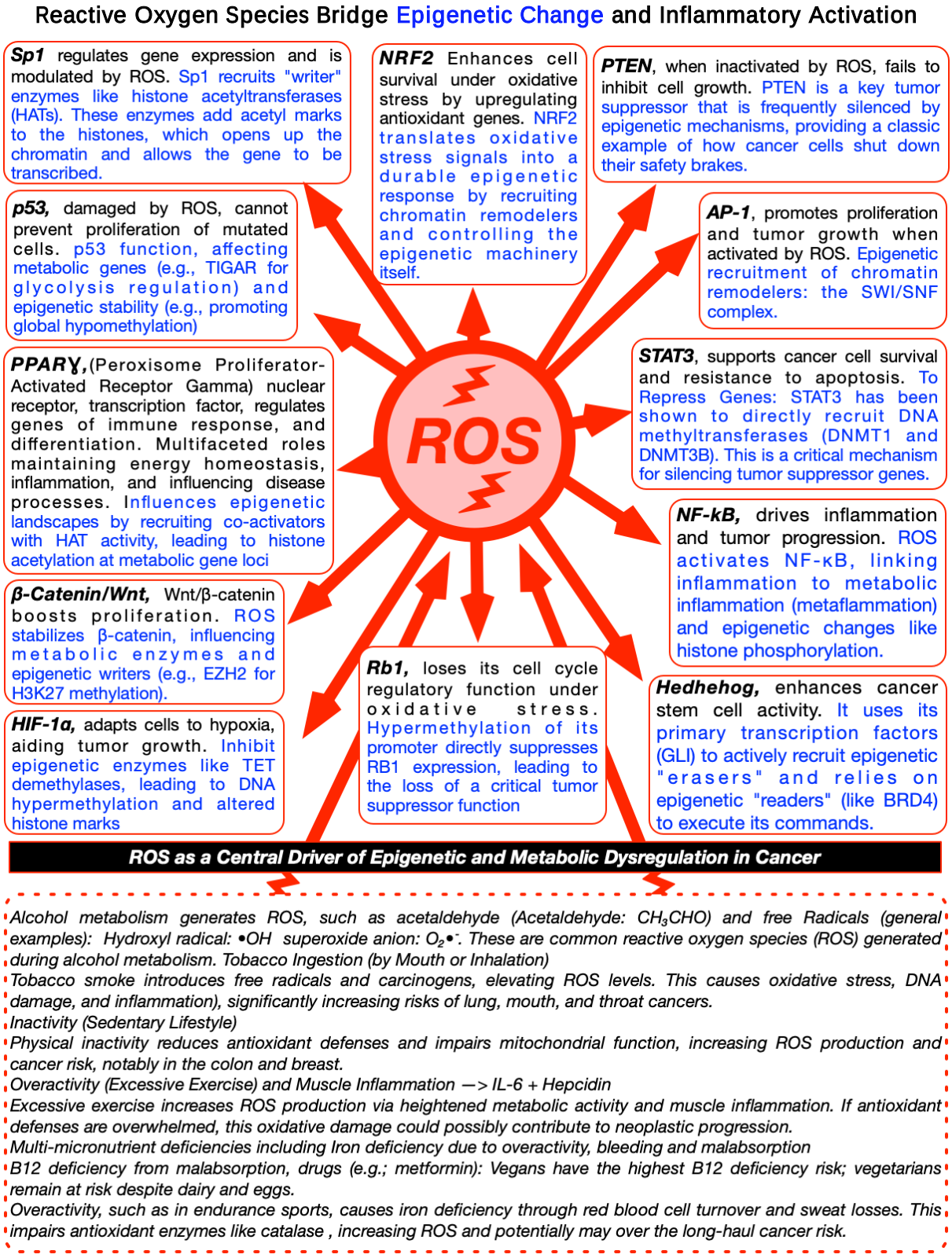

Figure 3 *Legend: This figure illustrates how oxidative stress, driven by reactive oxygen species (ROS), acts as a central upstream trigger, simultaneously activating epigenetic reprogramming (in blue) and inflammatory/metabolic signaling pathways that converge to promote the initiation of neoplasia, with the potential for progression to malignancy.*

Clinical note: *Early recognition and correction of ROS drivers, particularly alcohol ingestion, tobacco, asbestos exposure, obesity-associated or chronic inflammation, and iron deficiency (with or without anemia), may mitigate risk.*

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Reactive Oxygen Species Link Epigenetics and Inflammation (Figure 3)

Oxidative stress is linked to molecular injury, epigenetic reprogramming, and chronic inflammation. Reactive oxygen species act as second messengers, signaling to transcription factors and chromatin-modifying enzymes, altering inflammatory responses and gene regulation.[25] Persistent ROS induce stable DNA methylation and histone modifications, locking in gene expression patterns that predispose to neoplastic changes.[26,27,15] Physiologically, ROS modulate hypoxia-inducible factor (HIF) signaling, linking redox state to normal cellular adaptation.[28,29] Dysregulated ROS amplify HIF and inflammatory signaling, driving carcinogenic potential.[9,30]

Chronic oxidative stress disrupts the tumor-suppressor defenses of p53, which safeguards against DNA damage, RB1, which acts as a brake on the cell cycle, and PTEN, which blocks excessive growth signals. At the same time, it amplifies pro-cancer pathways: inflammatory signaling that promotes survival and proliferation, cell-to-cell adhesion changes that encourage invasion, and metabolic reprogramming that fuels tumor progression. These converge on the epigenome, shifting DNA methylation, histone modifications, and chromatin accessibility, silencing protective genes and unlocking growth programs.

Chronic inflammation and reactive oxygen species form self-reinforcing cycles, worsened by conditions such as gastritis, colitis, or iron deficiency, progressively lowering the threshold for oncogenic development over time.[31,32,33]

"Silent silencing" of tumor-suppressor genes precedes histologic dysplasia. At the same time, survival, metabolic, angiogenic, and immune evasion pathways lock in.[34,35,36,37] Initially reversible **Figure 5**, these changes may become permanent, explaining slow progression in premalignant lesions (Barrett's esophagus, colon adenomas, atypical breast lesions). Addressing upstream drivers (such as smoking, obesity, iron deficiency, and hyperhomocysteinemia) may not reverse epigenetic marks, but it may lower the malignant potential of progression.[22]

From Oxidative Stress to Epigenetic Lock-In

Chronic oxidative stress disrupts redox homeostasis, overwhelming antioxidant defenses and driving molecular reprogramming. Transcription factors (NF-κB, HIF-1α/HIF-2α, NRF2) stay active, and epigenetic marks lock in aberrant states, silencing tumor-suppressor genes, impairing DNA repair, and redirecting metabolism toward proliferation.[9,15,38] These changes, often silent for years, may predispose premalignant conditions (e.g., ductal/lobular carcinoma in situ, Barrett's esophagus, high-grade prostatic intraepithelial neoplasia) to dangerous neoplasia despite appearing stable.

Latency to cancer varies from 3 to over 20 years, with epigenetic changes preceding detectable genetic alterations and passing to daughter cells. Per Ames's triage theory, micronutrient deficiencies (iron, vitamin B_{12}, folate) prioritize survival over genomic maintenance, causing DNA damage and epigenetic shifts that set the stage for advanced neoplastic lesions.[39,40] Early ROS and inflammatory signaling rewire metabolism, angiogenesis, and immune evasion, consolidating via epigenetic lock-in with repressive histone and CpG methylation at tumor-suppressor loci, while oncogenic programs gain chromatin accessibility.

Iron- and 2-oxoglutarate-dependent demethylases are inhibited, stabilizing hypoxia signaling and suppressing anticancer mechanisms.[41,42] Chronic ROS from inflammation, smoking, obesity, or alcohol boosts NF-κB and HIF, fostering a tumor-friendly microenvironment.[43] Low folate and vitamin B_{12} impair DNA methylation, while iron deficiency silences anticancer genes.[44,23] Addressing these may not reverse epigenetic marks but can slow neoplastic progression.[44,41,45]

Premalignant lesions vary in progression risk. Lobular carcinoma in situ shows methylation changes like early breast cancer, marking an elevated risk.[46] Gallstone-related cholecystitis has low transformation risk unless high-risk features exist.[47] Bronchial squamous

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dysplasia or high-grade vulvar intraepithelial neoplasia progresses faster, within ~3 years, while indolent lesions may take >20 years.[48,49] Age, comorbidities, and lifestyle (smoking, alcohol, obesity) accelerate progression to oncogenesis.[47,48] Molecular alterations increase risk even in "low-grade" histology.[48]

Estimated Latency Periods for Progression from Premalignant Lesions to Overt Malignancy

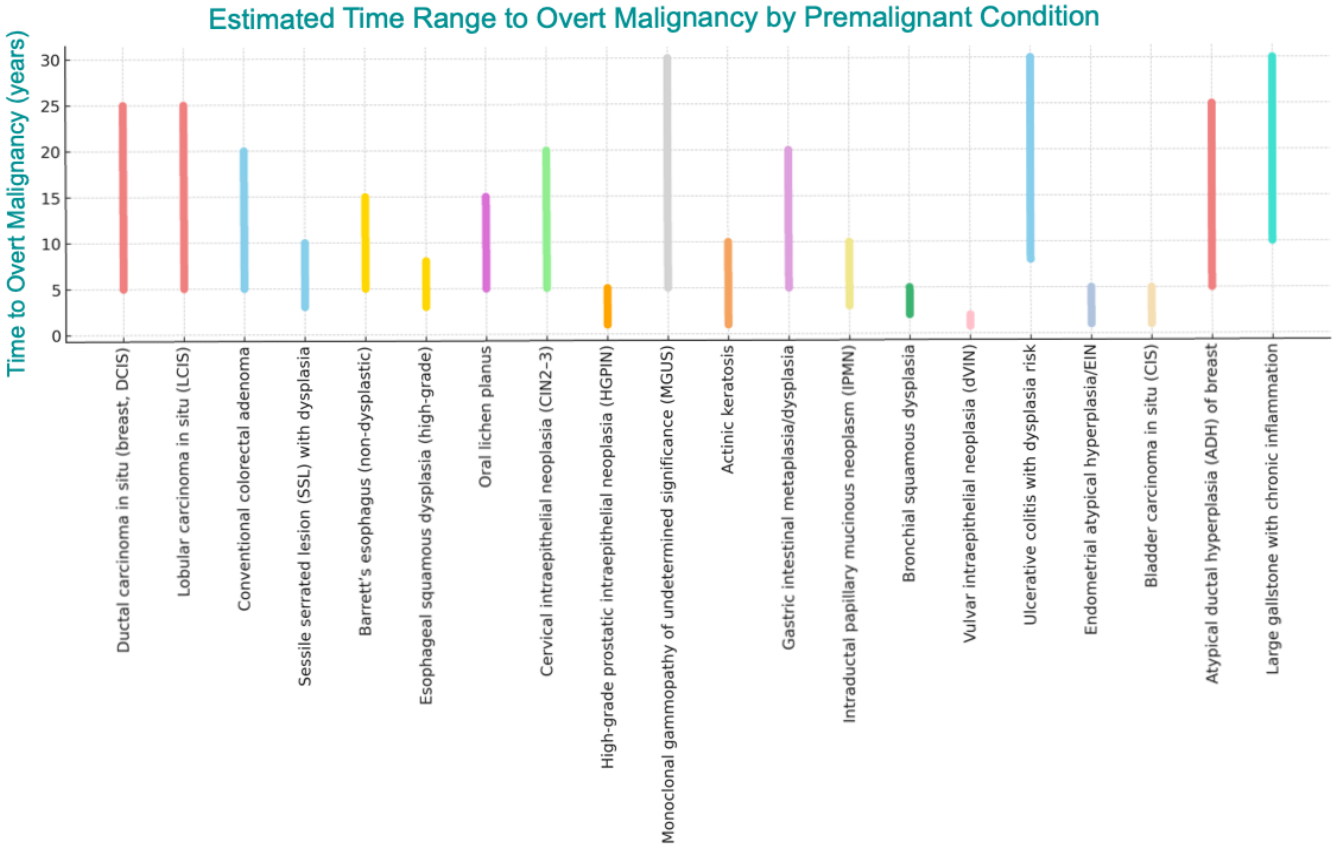

Figure 4 *Legend: Summarizes the estimated time intervals from diagnosis of selected premalignant conditions to the development of overt malignancy, based on published natural history and longitudinal cohort data. Each bar represents the approximate latency range (in years) observed for the specific lesion, highlighting substantial variability between conditions. Longer latency periods (e.g., lobular carcinoma in situ, large gallstone-associated chronic inflammation) suggest wider intervention windows. In contrast, shorter intervals (e.g., bronchial squamous dysplasia, vulvar intraepithelial neoplasia, high-grade PIN) underscore the need for closer surveillance. Values reflect composite ranges from multiple studies and may vary with patient age, comorbidities, and exposure to additional risk factors.*

Figure 4 and Table 1 summarize these estimates across diverse organ systems, including breast, colon, esophagus, prostate, bladder, pancreas, endometrium, oral mucosa, skin, and biliary tract. Each reflects composite ranges derived from natural history studies and longitudinal follow-up.

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Premalignant Lesions and Estimated Risks of Progression to Malignancy

Premalignant Lesion	Estimated Risk of Malignant Transformation	Reference
Ductal Carcinoma in Situ (DCIS)	If unmanaged, historical series suggest ~14–53% progress to invasive cancer over ≥10 years (low-grade ~35–50% over decades).	50,51
Lobular Carcinoma in Situ (LCIS)	Annual invasive breast cancer incidence ~1–2% (≈15–30% over 10–20 y) without chemoprevention.	52
Traditional Serrated Adenoma (Colorectal)	Dysplastic serrated polyp with significant malignant potential; complete excision and surveillance recommended.	53
Sessile Serrated Lesion with Dysplasia	High risk: series report frequent synchronous advanced neoplasia and not-infrequent coexistent carcinoma at diagnosis.	54,55
Barrett's Esophagus (Non-Dysplastic)	~0.12–0.3% per year to EAC; higher with dysplasia.	56,57
Esophageal Squamous Dysplasia (High-Grade)	Approx. 6–9% annual risk of ESCC; ~4% per year for mild–moderate.	58
High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)	Modern series: ~25% detection of carcinoma on repeat biopsy overall; higher (≈30–40%) if multifocal.	59,60
Oral Lichen Planus	Pooled malignant transformation risk ~0.5–1% (varies by subtype and criteria).	61
Cervical Intraepithelial Neoplasia (CIN3)	Long-term untreated CIN3 carries substantial risk; cohort estimates ~30%+ progression over extended follow-up.	62
Intraductal Papillary Mucinous Neoplasm (Pancreas)	Risk varies by type; ~5–10% over 5 y in branch-duct IPMN without high-risk features; higher in main-duct or with worrisome features.	63
Monoclonal Gammopathy of Undetermined Significance (MGUS)	Average progression ~1% per year to myeloma or related disorders.	64
Actinic Keratosis	Per-lesion annual progression to invasive SCC typically 0.025–0.6%; higher in high-risk patients.	65
Gastric Intestinal Metaplasia	Average annual gastric cancer risk ~0.25–0.6%; elevated with extensive IM, incomplete subtype, or H. pylori.	66
Bronchial Squamous Dysplasia (High-Grade)	High-grade and persistent lesions carry markedly increased risk of SCC on follow-up.	67
Vulvar Intraepithelial Neoplasia (VIN)	Transformation estimates vary; roughly 10–15% if untreated, higher in differentiated VIN.	68
Ulcerative Colitis with Low-Grade Dysplasia	Meta-analyses: CRC ~0.8%/y; advanced neoplasia ~1.8%/y following LGD.	69
Endometrial Atypical Hyperplasia / EIN	Concurrent carcinoma at hysterectomy ~30–50%; progression risk ~8% per y without treatment.	70
Bladder Carcinoma in Situ (CIS)	If untreated, up to ~50% progress to muscle-invasive disease; high-risk NMIBC category.	71
Atypical Ductal Hyperplasia (ADH)	~7% at 5 y; ~13% at 10 y; ~29–30% at 25 y (long-term cohort).	72
Chronic Cholecystitis with Large Gallstone	Absolute annual risk low (<1%/y), but large stones (>3 cm) confer distinctly higher gallbladder cancer risk.	73

Table 1 Legend: Premalignant Lesions

- *Premalignant Lesion: Name and description of the condition, including affected organ/tissue. Premalignancy does not condemn all lesions to become malignant.*
- *Estimated Risk of Malignant Transformation: Approximate progression rate to cancer, varying by grade, size, demographics, and treatment. Annual rates or lifetime risks are provided, not absolute predictions. Premalignant lesions signal chronic oxidative stress and epigenetic lock-in. Early intervention (local eradication or surgery) reduces progression risk.*[74]

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Epigenetic Regulation of Chromatin and Gene Expression

Epigenetic changes regulate gene activity through chromatin without altering the underlying DNA sequence. Histone tails in repressed chromatin (heterochromatin) carry marks (H3K27me3, H3K9me3), condensing DNA and blocking transcription. In active chromatin (euchromatin), acetyl marks (H3K27ac) loosen DNA, enabling transcription. "Reader" proteins (e.g., BET) recognize acetyl marks, recruiting transcription machinery. DNA methylation at CpG islands blocks transcription; unmethylated promoters stay open (Figures 6, 7).[75]

Normally dynamic, chromatin marks shift in response to changes in oxygen, nutrients, and redox balance. Persistent oxidative stress often leads to aberrant histone modifications and DNA methylation, thereby locking tumor suppressor loci and predisposing to oncogenic pathways. These reversible changes are key to risk stratification and therapy. In normal cells, histone marks (H3K4me3, H3K9me2/3, H3K36me2/3, H3K27me3) and DNA methyltransferases (DNMT1, DNMT3A/B) maintain regulation. Polycomb complexes add reversible repression via H3K27me3 **Figure 5**. In cancer, the aberrant methylation of CpG islands and deposition of the irreversible histone marks disrupt this balance, silencing tumor suppressors and driving oncogenesis.

Epigenetic Reprogramming of DNA Methylation Patterns in Normal Versus Cancer Cells

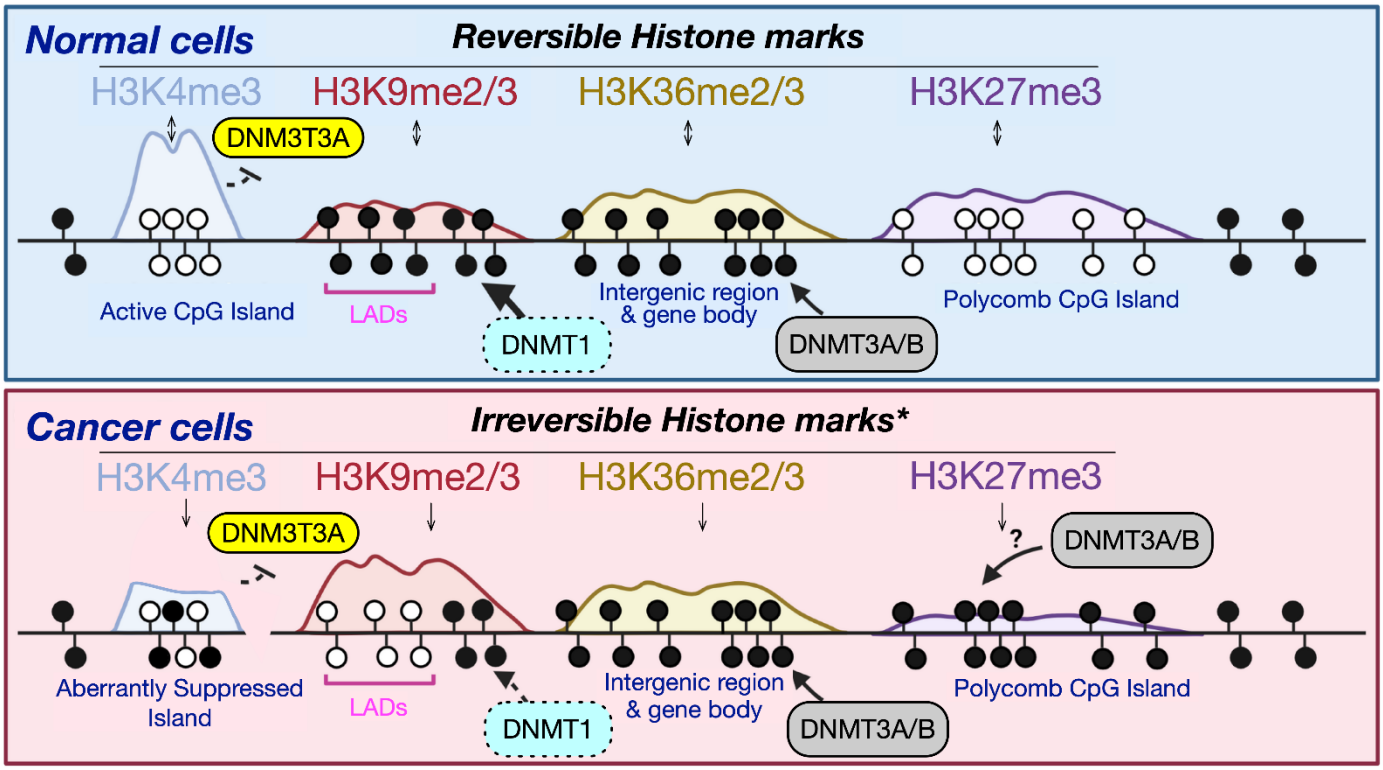

Figure 5 Legend: ***Epigenetic Reprogramming of Cellular DNA Patterns****: Normally Reversible (blue background) vs. Cancer Cells (pink background), Generally Irreversible (without therapeutic intervention). Image modified by Tisman. Original by Yinglu Li, Xiao Chen, and Chao Lu: https://doi.org/10.15252/embr.202051803*

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Figure 5 *Legend Summary as a Table*

Epigenetic Process	Normal Cell	Cancer Cell
H3K4me3 (Tag on histone showing active genes)	Found at active CpG islands, marking genes that are turned on; keeps DNA unmethylated so genes can work.	Less common at silenced CpG islands, linked to genes being turned off abnormally.
H3K9me2/3 (Tag on histone showing quiet regions)	Found in silent areas like gene bodies and LADs, helping to keep unwanted DNA inactive.	Still present but may be disrupted in LADs, contributing to DNA instability in cancer.
H3K36me2/3 (Tag on histone during gene activity)	Found in active gene areas, helping genes work properly and adding methyl groups to DNA.	Reduced in some areas, leading to messy gene activity and cancer changes.
H3K27me3 (Tag on histone for temporary gene silencing)	Found at CpG islands controlled by Polycomb proteins, keeping genes off but reversible.	Still present but can get extra methyl groups, locking genes off permanently in cancer.
DNA methylation at active CpG islands	Low methylation, kept open by H3K4me3 tags; DNMT3A enzyme is present but doesn't add methyl groups.	High methylation by DNMT3A, turning off genes (e.g., tumor suppressors) that should stay on.
DNA methylation at LADs and gene bodies	High methylation by DNMT1 and DNMT3A/B, keeping these areas quiet with H3K9me2/3 tags.	Low methylation, possibly due to lost DNMT activity, causing instability and gene activation.
DNA methylation at Polycomb CpG islands	Little to no methylation, allowing flexible gene control by Polycomb proteins.	Extra methylation, possibly by DNMT3A/B, locking genes off and aiding cancer growth.

Figure 5 Legend continued:

Panel A

Initial adaptation: *Under stress (such as iron deficiency, hypoxia, inflammation, or nutrient loss), normal cells reprogram their metabolism and epigenetics to conserve energy and survive.*

During chronic stress, followed by the epigenetic lock-in effect*, temporary survival (histone and DNA) marks become fixed, silencing tumor-suppressor genes and rewiring growth pathways.*

Panel B

****Oxidative stress can make usually reversible histone marks functionally irreversible by inactivating the enzymes that remove them or by inducing direct oxidative modifications to histone residues, which standard epigenetic enzymes cannot repair. This shift causes persistent changes in chromatin and gene expression, which persist until the histones themselves are degraded or replaced, potentially culminating in the neoplastic conversion to an oncogenic state.*

Clinical meaning: *Cancer can be seen not as an alien process, but as a normal cell's prolonged survival strategy that has become permanently maladaptive without effective therapy.*

Definitions:

CpG Islands*: Specific DNA regions with many C and G letters close together, often near genes that can be turned on or off.*

LADs *(Lamina-Associated Domains): Areas of DNA attached to the cells inner lining (nuclear lamina), usually kept quiet and tightly packed.*

Polycomb CpG Islands: *DNA regions where Polycomb proteins help temporarily turn off genes, often involved in development.*

DNMTs *(DNA Methyltransferases): Enzymes (e.g., DNMT1, DNMT3A, DNMT3B) that add methyl groups to DNA, affecting gene activity.*

Histone Modifications: *Chemical changes to histone proteins (e.g., H3K4me3, H3K9me2/3) that act like switches to control DNA accessibility and gene expression.*

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Epigenetic Histone Writers, Readers, and Eraser Enzymes

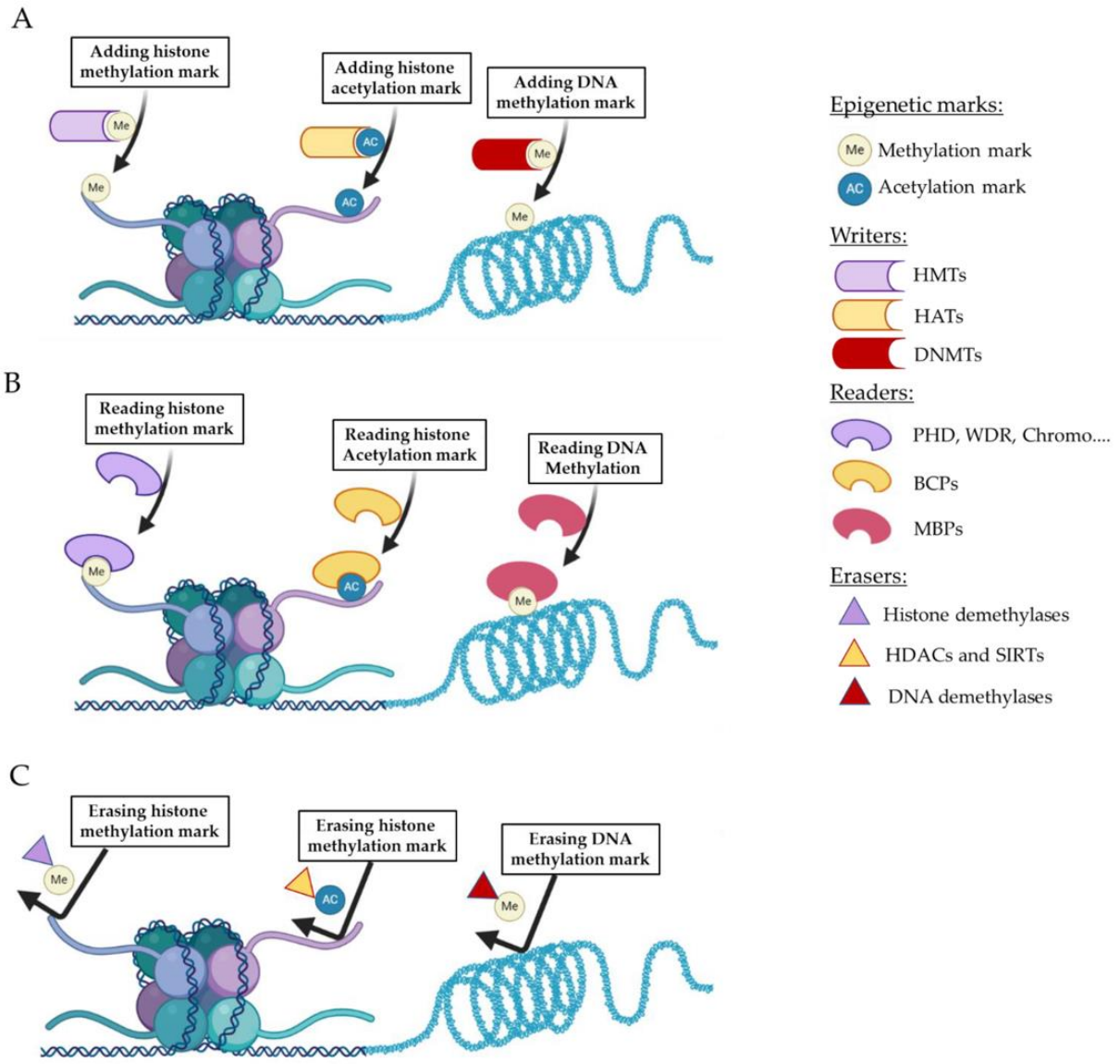

Figure 6 Legend: *Coordinated roles of epigenetic writers, readers, and erasers in chromatin regulation. Writers add chemical marks (methyl, acetyl) to histones or DNA, altering chromatin structure and gene transcription. Readers recognize these marks and recruit complexes that activate or repress transcription. Erasers remove the marks, restoring chromatin plasticity. Together these modules regulate gene expression and cell identity; their disruption can drive oncogenesis and represents a target for epigenetic therapy (adapted from Ghiboub et al. doi:10.3390/jpm11050336).*

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Correlation between Histone Modifications and Distinct Neoplastic Entities

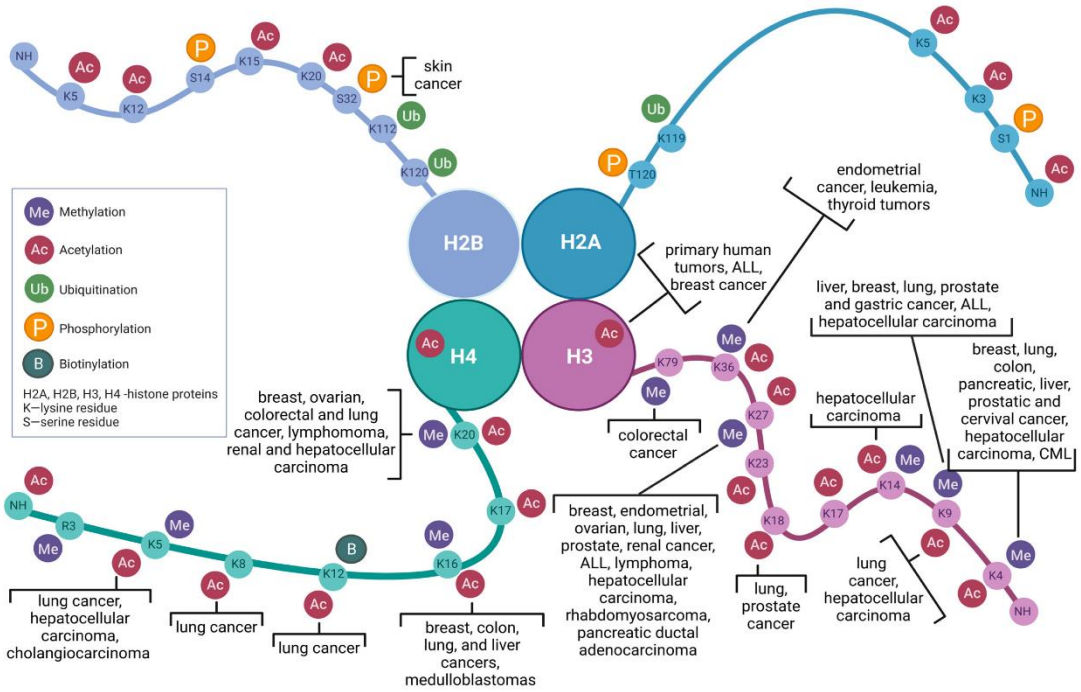

Figure 7 Legend: *Histone Post-Translational Modifications in Cancer. These schematic maps show post-translational modifications (PTMs) on N-terminal tails of histones H2A, H2B, H3, and H4 in human malignancies. PTMs include methylation (Me), acetylation (Ac), ubiquitination (Ub), phosphorylation (P), and biotinylation (B), color-coded and mapped to lysine (K) or serine (S) residues. These modifications regulate oncogenesis via epigenetic control. Labeled boxes link specific PTMs (e.g., H3K27me3, H3K4me3, H3K9me, H4K20me) to cancer types, showing correlations with transcriptional activation or silencing. The "histone code" underscores diagnostic relevance in neoplasia and cancer biology. Image from Szczepanek, J.; Tretyn, A. MicroRNA-Mediated Regulation of Histone-Modifying Enzymes in Cancer: Mechanisms and Therapeutic Implications. Biomolecules 2023, 13, 1590.*

DNA Methylation: Gene Silencing Mechanism. DNA methylation (Figure 5) adds methyl groups to cytosine in CpG dinucleotides at gene promoters, silencing transcription when the cytosine is methylated and enabling it when the cytosine is unmethylated. In cancer, tumor suppressors are often hypermethylated, while oncogenes are frequently hypomethylated, distinguishing malignant from normal cells.[76] Therapeutically, histone modifications (Figures 6, 7) are targeted using HDAC inhibitors for cutaneous T-cell lymphoma, B-cell lymphomas, and multiple myeloma. Methyltransferase and demethylase inhibitors are in development to reactivate silenced tumor suppressors (Figure 2).[76]

Non-Coding RNAs: Epigenetic Regulators

Non-coding RNAs are RNAs that do not encode proteins; they assist in regulating gene expression by interacting with the same epigenetic tools that add or remove chemical tags on DNA and histones. They function like address labels, guiding these tools to the correct locations in the genome.

There are many different types of ncRNAs, some of which are included in **Table 2.**

Non-coding RNAs (ncRNAs) play a crucial role in normal metabolic and epigenetic regulation, and their dysregulation is associated with various diseases. An imbalance of ncRNAs is associated with cancer, cardiovascular, neurologic, and autoimmune disorders, often by turning **off tumor-suppressor** programs or activating **oncogenic** ones. Circulating miRNAs and tumor-specific lncRNAs/circRNAs are valuable for early detection, risk assessment, and disease monitoring because they are tissue-specific and, especially for circRNAs, highly stable.
Therapeutically, strategies involve miRNA **mimics** and **inhibitors**, as well as antisense or siRNA drugs targeting oncogenic lncRNAs or circRNAs. These

can be combined with epigenetic agents (EZH2, DNMT, HDAC, and BET inhibitors) to disrupt RNA-guided gene silencing; the lncRNA–EZH2 axis is a primary target. Though early new laboratory techniques for measuring and interacting with the metabolism of these ncRNAs are extremely promising, except for a minority of new tests, the science remains investigational, but not for long.

Mechanistic example: **EZH2/PRC2** is a gene-silencing complex. Many lncRNAs bind to EZH2 and direct it to promoters, where it deposits the repressive **H3K27me3** mark on histone H3, turning genes off. Blocking EZH2—or the lncRNA–EZH2 interaction—can activate tumor-suppressor genes.

In summary, ncRNAs serve as "address labels" that guide epigenetic machinery to specific locations, thus regulating tumor suppressors and oncogenes. This dual function makes them important **biomarkers** and **potential drug targets**, including when combined with existing epigenetic therapies.[76]

Table 2 Major Classes of Non-Coding RNAs in Epigenetic Regulation

Type of ncRNA	How it Works (Mechanism)	Example Function	Medical Relevance
Long non-coding RNAs (lncRNAs)	Act as guides to bring chromatin enzymes (e.g., PRC2) to DNA; act as scaffolds to assemble complexes; form RNA–DNA triplexes	Fendrr: controls histone marks during heart development	Loss leads to lethal heart/body wall defects in mice; downregulated in many cancers
Enhancer RNAs (eRNAs)	Transcribed from enhancers; help enhancers and promoters loop together; stabilize RNA polymerase binding	eRNAs in muscle development guide histone acetyltransferases	Dysregulated eRNAs linked to abnormal growth and cancer
Natural Antisense Transcripts (NATs)	Made from the opposite DNA strand; can silence the matching gene or recruit repressors like PRC2	HOTAIR: recruits PRC2 and LSD1 to silence tumor suppressors	Overexpressed in cancers; promotes metastasis
Small ncRNAs (sncRNAs) – microRNAs (miRNAs), piRNAs	miRNAs: bind mRNA, block translation or trigger degradation; can indirectly regulate epigenetic enzymes. piRNAs: silence mobile DNA (transposons) in germ cells	miR-29: regulates DNA methyltransferases	miRNAs altered in many cancers; piRNA defects cause infertility
Circular RNAs (circRNAs)	Closed-loop RNAs; act as sponges for miRNAs or recruit enzymes like EZH2	circLRIG3: promotes cancer by scaffolding EZH2 and STAT3	Overexpressed in hepatocellular carcinoma and breast cancer
Special Case: Xist (lncRNA)	Coats one X chromosome in females and recruits silencing complexes (PRC1/PRC2)	Xist: essential for X-inactivation	Explains dosage compensation; disruption causes developmental abnormalities

Table 2 Legend: *Non-Coding RNAs (ncRNAs) in Epigenetic Regulation. This table outlines a sampling of ncRNA types influencing gene expression via epigenetic mechanisms. ncRNAs guide chromatin-modifying enzymes, stabilize enhancer-promoter interactions, or silence genes through antisense pairing, regulating chromatin accessibility and transcription. Examples and their medical relevance highlight roles in developmental abnormalities, infertility, and possible irreversible progression to uncontrollable neoplasia.*

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Clinical Significance of ncRNAs

Epigenetics, metabolism, and ncRNAs form an integrated regulatory network hijacked in cancer to promote survival and proliferation. Biomarkers: Circulating miRNAs enable non-invasive detection of colorectal, breast, and lung cancers.[77,79] Therapeutics: miRNA mimics (e.g., MRX34) and inhibitors (e.g., Miravirsen) show promise in oncology and virology, though some trials (e.g., MRX34) halted due to immune-related issues.[80, 86] Environmental Coupling: Hypoxia, oxidative stress, and nutrient status alter ncRNA expression, impairing DNA repair and immune surveillance, fostering premalignancy.[87,89]

Integrated Epigenetic Control. DNA methylation, histone modifications, and ncRNAs interact in cancer and metabolic reprogramming.[90,91] lncRNAs guide chromatin enzymes (e.g., PRC2/EZH2) to silence genes.[92,93] H3K36me3 directs DNA methylation via DNMT3B.[94,95] Promoter methylation regulates miRNA/lncRNA expression, altering chromatin effects.[96,97] Chronic stress (oxidative, iron dysregulation, inflammation) represses tumor suppressors, activates survival pathways, and supports carcinogenesis.[98, 99] Epigenetics links environmental stress to long-term cellular memory, driving malignancy years before clinical detection.

Clinical Vignettes Highlighting the Dangerous Potential of Hidden Epigenetic Metabolism

Patient 1) A 43-year-old woman with occasional minimal intermittent fatigue and joint discomfort, normal CBC and blood chemistry panel. The physician assistant exam, confirmed by the physician, is normal. The patient is rescheduled for another presumed well-patient exam a year later.

She returns instead a month later to discuss an abnormal mammogram revealing a 0.7 cm partially microcalcified tissue-distorting lesion, which was confirmed by excisional biopsy as atypical lobular hyperplasia. Pre-op hospital blood panel revealed a low serum ferritin of 13 µg/L as well as a normal CBC, notably Hb of 12.8 with a normal MCV and RDW. Hematology consultation confirmed the diagnosis of latent iron deficiency. The pathology report noted that such breast lesions have a 25-30% risk of developing invasive lobular or ductal breast cancer within 25 years. She was immediately placed on oral iron replacement therapy. Additional therapy with three years of low-dose, 5 mg/d tamoxifen adjuvant therapy was discussed.

Epigenetic Interpretation-1: Chronic iron deficiency is a strong driver of reactive oxygen species (ROS). This patient should be monitored not only for iron status but also for other correctable micronutrient deficiencies, including vitamin B12, folate, and vitamin D, as well as for hyperhomocysteinemia. Identifying and correcting these abnormalities helps reduce oxidative stress and its downstream epigenetic effects.

Patient 2) A 64-year-old Asian Indian man, a semi-professional pickleball player with a 10-year history of Barrett's esophagus (premalignant esophageal metaplasia without dysplasia), was diagnosed with chronic latent iron deficiency (see **Figure 8**). Ferritin levels were low-normal (<50 µg/L) for several years, eventually dropping to 10 µg/mL, while he consistently maintained normal hemoglobin levels. Around the same time, serum B12 fell to 174-276 pg/mL, possibly related to PPI-induced achlorhydria impairing iron and B12 absorption, as well as B12 malabsorption from metformin use for DMII. Concurrently, the patient was diagnosed with early bilateral symmetrical peripheral neuropathy involving the lower extremities, consistent with DMII-associated peripheral neuropathy versus subacute combined degeneration due to B12 deficiency, as indicated by EMG. However, these conditions cannot be differentiated by EMG.

No occult GI blood loss was confirmed. The patient intermittently self-treated over the past 10 years with oral iron for fatigue and consumed a crunchy Asian Indian snack (Fryums), along with a typical American diet. We hypothesized that Fryums ingestion may indicate a form of iron deficiency-related pica.

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Epigenetic Interpretation-2: IV iron and daily oral methylcobalamin (500 µg) were initiated to correct deficiencies and to counteract epigenetic changes driven by chronic oxidative stress in the setting of Barrett's esophageal metaplasia and micronutrient deficiency. The therapeutic goal is to lessen oxidative injury and thereby reduce the risk of progression from premalignant dysplasia to malignancy.

Barrett's **Esophageal Metaplasia in a Pickleball Player with Prolonged Latent Iron Deficiency and Newly Diagnosed Latent B12 Deficiency from Patient Vignette 2**

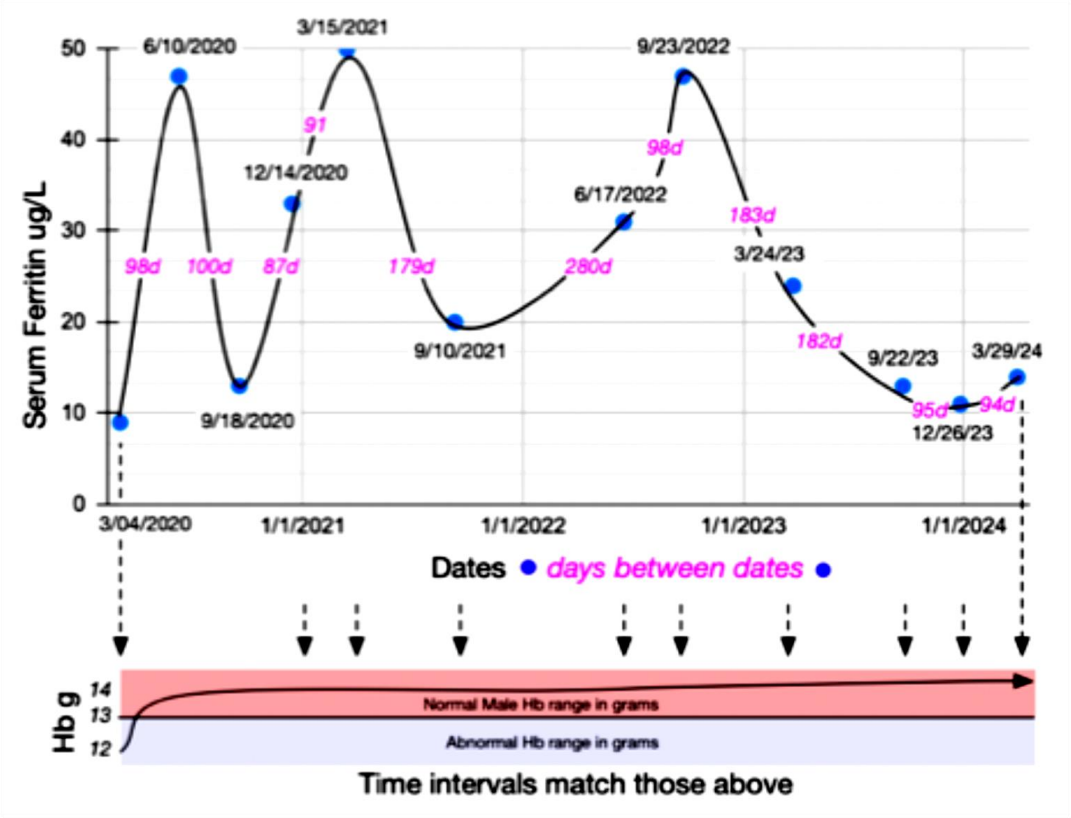

Figure 8 Legend: *Time-series of serum ferritin (µg/L; blue points) and hemoglobin (g/dL; pink band) in a 64-year-old Asian Indian semi-professional pickleball player with Barrett's esophagus without dysplasia. Ferritin fluctuated but was predominantly <50 µg/L with a nadir of 10 µg/L, while hemoglobin remained 13–14 g/dL. Probable contributors to iron and cobalamin deficiency include proton–pump–inhibitor–related hypochlorhydria, metformin use for type 2 diabetes (associated with B12 malabsorption), and high-volume daily exercise with sweat iron losses and episodic cytokine-driven (e.g., IL-6) hepcidin elevations. The patient frequently consumed "Fryums," a behavior resembling starch-related pica described in iron deficiency. Management included intravenous iron repletion and 1,000 µg cyanocobalamin administered subcutaneously, followed by daily oral B12 (1,000 µg), with the intent to correct latent deficiencies, mitigate oxidative and epigenetic stress, and reduce the risk of progression from Barrett's metaplasia to dysplasia or malignancy. A recent diagnosis of oral lichen planus responded to a topical steroid mouthwash; this lesion may also be associated with iron and B12 insufficiency.*

Oxidative Stress–Driven Epigenetic Memory: The Point of No Return in Cancer Development?

The following schematic **Figure 9** traces a stepwise path from a buffered, reversible stress response to fixed, malignant programming. Transient oxidative stress activates HIFs, NF-κB, and NRF2, with the epigenome initially preserved. When reactive oxygen species persist, the stress becomes chronic, and the epigenetic machinery installs repressive DNA and histone marks (e.g., H3K9me3, H3K27me3) while activating marks (e.g., H3K4me3). **Figure 5** shows a decline, thereby silencing tumor-suppressor pathways. Non-coding RNAs help target these complexes, creating an "epigenetic memory" that can persist even after the original stress has subsided. The result is clonal expansion with repurposed autophagy (reuse

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of the cell's own proteins), which supports neoplastic metabolism and contributes to treatment resistance, ultimately possibly leading to malignancy. Importantly, each tier in this sequence represents a druggable checkpoint. Hypomethylating agents, HDAC and EZH2 inhibitors, BET inhibitors, and autophagy modulators can partially reset or block specific steps, setting up the therapeutic sequence that follows.

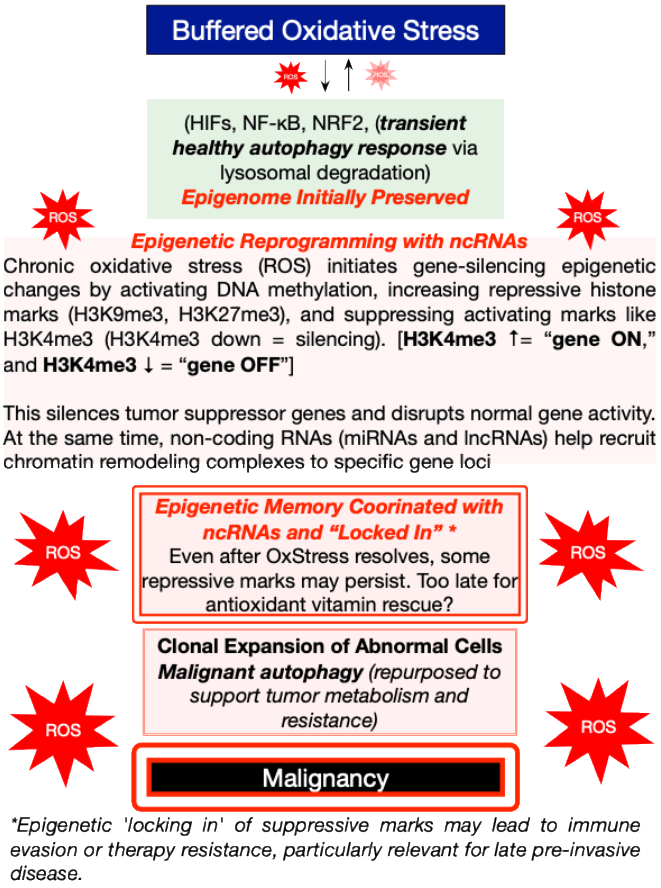

Figure 9 Legend: *Cellular Trajectory to Malignant Transformation. This schematic illustrates the progression from buffering transient oxidative stress to irreversible epigenetic lock-in. Blue box: Mild ROS is neutralized by antioxidants and regulators (HIFs, NF-κB, NRF2), with transient protective autophagy maintaining redox balance. Green box: Stable epigenome with minimal DNA/histone changes under maintained homeostasis. Pink box 1: Persistent ROS triggers repressive chromatin remodeling (H3K9me3, H3K27me3) and DNA methylation, silencing tumor suppressors, aided by ncRNAs (miRNAs, lncRNAs) guiding modifying complexes. Pink box 2: Post-stress, ncRNAs sustain silencing via PRC2, DNMTs, and HDACs, locking genes "off" with persistent marks, potentially resisting reversal in advanced stages. Black box: Malignant clones repurpose autophagy for tumor metabolism, survival, therapy resistance, invasion, and immune evasion.*

Why This Matters for Physicians and Patients

Clinicians must recognize that "normal" laboratory results may mask oxidative stress and epigenetic changes associated with iron deficiency, folate/B12 insufficiency and hyperhomocysteinemia, inflammation, or environmental exposures, thereby increasing the risk of carcinogenesis (Figure 3). These reversible gene expression alterations, rather than DNA mutations, shift prevention and early detection strategies, prompting therapies to reset epigenetic landscapes before irreversibility.[100,101]

Epigenetic Therapy I: DNA Methylation Approaches. CpG hypermethylation silences tumor suppressors reversibly.[100,101] DNMT inhibitors (e.g., azacitidine, decitabine) trap methyltransferases, decreasing methylation over multiple divisions to reactivate differentiation and apoptosis genes,

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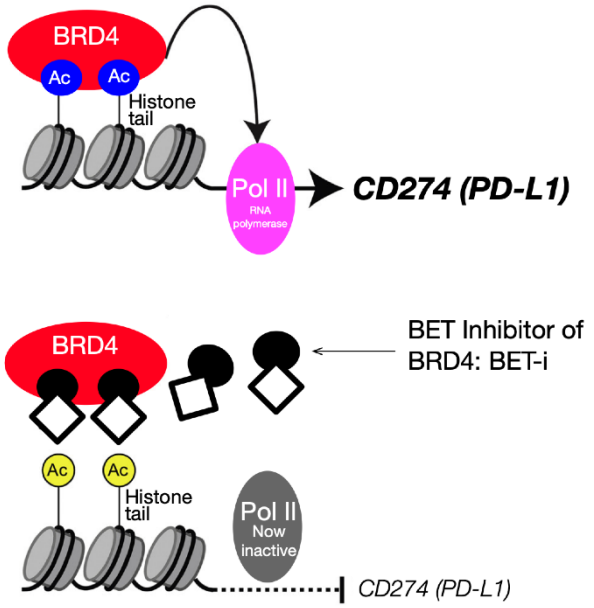
used in myelodysplastic syndromes and AML.[102,103] These broad effects cause cytopenias but show potential for epigenetic reset.[86,103,104]

Epigenetic Therapy II: Histone Acetylation Control. Cancer reduces tumor suppressor acetylation while enhancing oncogenic activity.[105] HDAC inhibitors (e.g., vorinostat, romidepsin for T-cell lymphoma; belinostat, panobinostat for multiple myeloma) maintain open chromatin, thereby reactivating genes and deriving benefits from expression restoration.[106-111] Toxicities include fatigue, cytopenias, and cardiac effects.

Epigenetic Therapy III: BET Inhibitors and Super-Enhancers Control. BET inhibitors (e.g., JQ1, OTX015/mivebresib) target BRD4, disrupting acetyl-lysine binding at oncogenic super-enhancers to suppress MYC and inflammatory programs, showing antitumor activity (**Figure 10**).[112-117] They also lower PD-L1, enhancing immunity and supporting immunotherapy combinations.[118-120]



BET inhibitors (BET4i), lower both PD-L1 on tumor and immune cells and PD-1 on T cells, contributing to a less immunosuppressive tumor microenvironment and enhanced anti-tumor immunity. RNA polymerase II stalls or pauses its activity.

Figure 10. Legend: *BET Inhibition Reduces PD-L1 via BRD4 Displacement. BRD4 binds acetylated histone tails, recruiting RNA polymerase II to transcribe CD274 (PD-L1), promoting immune evasion in tumors. BET inhibitors (e.g., JQ1, OTX015/MK-8628) displace BRD4, halting CD274 transcription, reducing PD-L1 expression, and enhancing antitumor immunity by creating a less immunosuppressive tumor microenvironment.*[113,114,116-118,121] *BRD4 enriches at super-enhancers, driving oncogene expression (e.g., MYC, PD-L1) to sustain malignancy and immune evasion. BET inhibitors collapse super-enhancer activity, selectively downregulating oncogenes.*

Clinical Applications. BET inhibition sensitizes triple-negative breast cancer to PARP inhibitors in the absence of homologous recombination deficiency[122]. It modulates tumor immunity by reducing PD-L1 expression, reprogramming tumor-immune interactions, and supporting antitumor responses with context-dependent effects on innate immunity.[118-120]

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BET4 Inhibition Reverses Tumor Immune Evasion by Blocking PD-L1/PD-1 Signaling

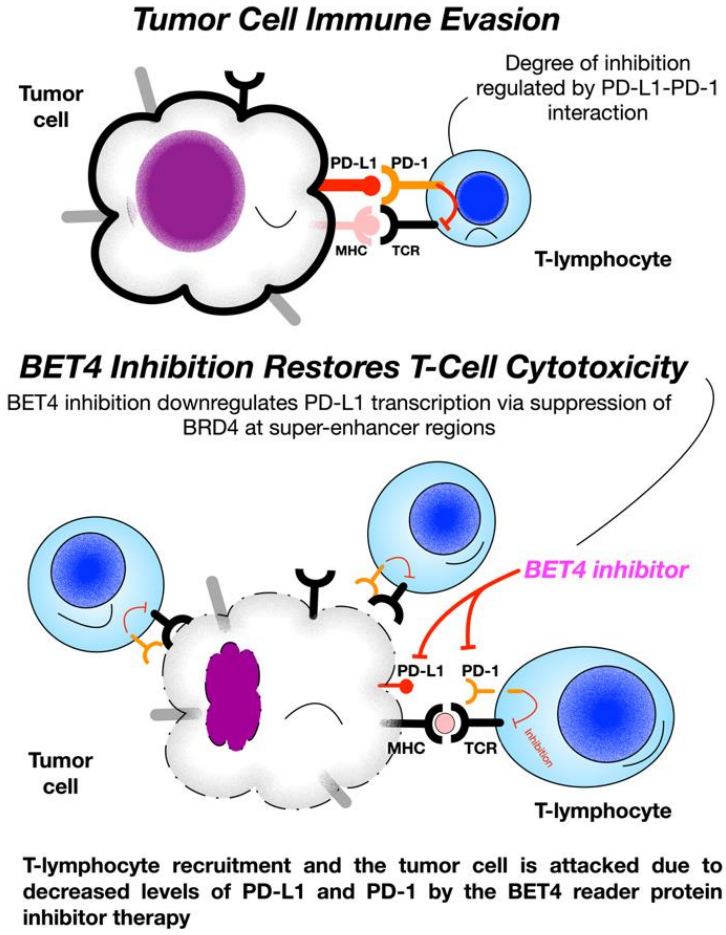

Figure 11. Legend: *BET Inhibition Restores Antitumor Immunity. Tumor cells evade immunity via PD-L1 binding to PD-1 on T cells, suppressing cytotoxicity. BET inhibitors reduce BRD4-driven PD-L1 transcription at super-enhancers, decreasing PD-L1 expression, enhancing T-cell recruitment and tumor cell killing, and reversing immune suppression.*[113, 116-118, 121]

BET and EZH2 Inhibitors. BET inhibitors (e.g., JQ1, OTX015) target NUT midline carcinoma, AML, and lymphomas by suppressing MYC, with toxicities like thrombocytopenia and fatigue.[106,112,116,117,123,124] EZH2, in PRC2, deposits H3K27me3 to silence tumor suppressors; tazemetostat reverses this, approved for epithelioid sarcoma and follicular lymphoma (~60% efficacy with mutations, ~30% without), promoting differentiation with manageable toxicities (fatigue, nausea, cytopenias).[13,125-130]

Epigenetic Therapy and Oxidative Stress. DNMT, HDAC, BET, and EZH2 inhibitors reverse epigenetic marks/scars caused by oxidative stress and deficiencies (e.g., iron, folate, B12), thereby reactivating genes that promote differentiation or apoptosis.[19,98,99,131,32] Preventing deficiencies may halt premalignant progression.[91]

Conclusion

Chronic oxidative, inflammatory, and hypoxic stress aberrantly activates survival pathways (HIF, NF-κB) and epigenetic modulators (H3K27me3, H3K9me3, CpG methylation; see Figure 5). This sustained imbalance produces epigenetic lock-in, establishing stable oncogenic programs.[18,42,100,133-136] Restoring and maintaining normal redox and nutrient balance is central to prevention.

Clinical Implications: Epigenetic reprogramming can occur silently in asymptomatic patients with early micronutrient deficiencies, often undetected by routine laboratory tests and parameters, and only becomes apparent after premalignant or malignant lesions are identified. The latest "Multi-omics" and DNA-methylation assays, now available for research and certain clinical settings, can identify many

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"premalignant signatures" in tissue, blood, urine, fecal matter, and other samples.[137] Routine, though not always used, biochemical screening for iron status (Hb reticulocyte index, ferritin, directly measured TSAT, and sTfR or the sTfR/log ferritin index), serum homocysteine, and vitamins B12, red blood cell folate, B6, and D helps detect early, hidden, and correctable causes of oxidative stress.

A Medical Call to Arms Regarding Potential Neoplasia Due to Latent Iron Deficiency

In India, 31.5% of women and 32.7% of children have latent iron deficiency despite normal hemoglobin values.[137]

In the USA, according to the NHANES 2017–2020 (pre-pandemic) adult cohort study summary (n=8,021), 1 in 4 participants is confirmed to have latent iron deficiency.[1] Yes, **26%**, a key finding. Iron deficiency (among adults without anemia, heart failure, chronic kidney disease, or current pregnancy) was defined as latent iron deficiency. New physiological work strongly suggests that serum ferritin levels below 50 µg /L in both men and women should prompt screening for iron deficiency (see Part III of this Trilogy).

The NHANES study results for the USA were conducted on a representative sample of the general, noninstitutionalized U.S. population.

- Absolute iron deficiency: 11% (95% CI, 10–11)
- Functional iron deficiency: 15% (95% CI, 14–17)

Absolute iron deficiency was defined as serum ferritin <30 ug/L, regardless of transferrin saturation (TSAT).

Functional iron deficiency was defined as: TSAT <20% with ferritin ≥30 ng/mL.

Clinical Takeaway

Roughly 1 in 4 U.S. adults (possibly more) without anemia meet criteria for iron deficiency by ferritin/TSAT laboratory analysis, supporting routine consideration of iron studies even when hemoglobin is **normal.**[1]

Diagnostic Clinical Pearl

Pagophagia, the compulsive ingestion and chewing of ice, occurs in 11–56% of patients with iron deficiency and usually resolves after iron repletion.[138-141] Because patients rarely volunteer these behaviors, clinicians should ask directly about pica and its variants.

Clinical clues include:

- Routinely requesting super-sized soft drinks with extra ice
- Freezing water bottles to chew on the ice
- Geophagia: ingesting clay "cookies"
- Eating cornstarch (e.g., Argo) directly from the box
- Chewing dry, uncooked noodles
- Ingesting large amounts of sodium polystyrene sulfonate (Kayexalate) powder (one report)
- Impulsive chewing of rubber bands

Cultural and individual patterns may also appear. For example, one patient with Barrett's metaplasia (**Figure 8**) reported frequent intake of crunchy fried starch snacks ("Fryums"), while another consistently ingested fresh Xerox paper.[141]

Many drivers of oxidative stress are reversible (see Figure 3) and should be identified early to prevent progression to irreversible injury. Proactive inquiry by clinicians and staff is essential to detect the subtle, early manifestations of occult iron deficiency, the most common cause of potentially severe yet frequently unrecognized chronic oxidative stress.

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