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Transient Molecular Intervention, Persistent Gene Regulation: A Mechanistic Theory of Chromatin Memory, Feedback Stabilization, and Reversibility in Therapeutic Epigenome Editing

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Abstract

Therapeutic epigenome editing creates an unusual temporal problem: the molecular editor may be present only briefly, whereas the regulatory state established during that exposure can persist long after the initiating intervention has disappeared. Durable repression after transient delivery has now been demonstrated in several experimental settings, yet persistence is not an intrinsic consequence of depositing an epigenetic mark. Regulatory outcomes vary with locus architecture, chromatin context, effector design, cell state, proliferation, and the molecular processes that maintain or erase the installed state. This article develops a mechanistic account of post-editing persistence that distinguishes the duration of editor exposure from the lifetime of the resulting regulatory state. It argues that durable gene regulation should be understood as a trajectory emerging after editor withdrawal, governed by the balance between local chromatin reinforcement, replication-coupled inheritance, transcriptional feedback, competing regulatory inputs, and active or passive erasure. The account further separates persistence from irreversibility: a regulatory state may remain stable for prolonged periods while retaining molecular routes to reactivation. This distinction has consequences for therapeutic design, because insufficient persistence can eliminate benefit whereas excessive or poorly reversible persistence may create a different safety problem. A mechanistically credible evaluation of therapeutic epigenome editing therefore requires longitudinal evidence after verified editor clearance, measurements that connect chromatin state with transcriptional function, and perturbations capable of discriminating self-maintenance from continued exposure or other explanations.

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Introduction

Programmable epigenome editing has expanded the concept of genome engineering beyond alteration of DNA sequence. Catalytically inactive or otherwise repurposed DNA-targeting proteins can recruit transcriptional repressors, activators, DNA methylation machinery, demethylation machinery, or chromatin-modifying activities to selected genomic regions, creating experimentally controllable changes in gene regulation without requiring a sequence-changing lesion (McCutcheon *et al.*, 2024). This capability has made epigenome editing useful both for interrogating regulatory mechanisms and for developing therapeutic strategies in which abnormal expression might be corrected while leaving the underlying nucleotide sequence intact. Its translational significance, however, depends on properties that are not captured by the initial magnitude of gene repression or activation. Among the most important is whether the edited regulatory state survives after the molecular machinery that created it is no longer present (Heller *et al.*, 2026).

Evidence that transient intervention can produce extended regulatory effects has shifted this question from theoretical possibility to mechanistic problem. In mice, transient delivery of an engineered transcriptional repressor targeting hepatic *Pcsk9* produced repression that persisted for many months and remained detectable after experimentally induced liver regeneration; CRISPR-based transcriptional-memory systems have likewise demonstrated that temporary editor expression can install repressive states maintained through cell division and differentiation (Nuñez *et al.*, 2021; Cappelluti *et al.*, 2024). Earlier targeted methylation experiments in primary human breast cells also showed that promoter methylation and associated repression could remain after disappearance of the editing construct (Saunderson *et al.*, 2017). These observations establish that editor lifetime and regulatory-state lifetime can be uncoupled. They do not establish that this uncoupling occurs at every locus, with every effector, or through a single molecular mechanism.

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That distinction matters therapeutically. A transient molecular exposure is attractive because it can limit the period during which a programmable editor can interact with the genome. Yet reduced exposure does not automatically mean reduced biological consequence. Conversely, avoidance of a permanent sequence modification does not itself demonstrate safety. Studies of contemporary sequence-editing systems in human hematopoietic stem cells illustrate why the molecular consequences of an intervention must be characterized directly rather than inferred from its technological category (Fiumara *et al.*, 2024). Epigenome editing introduces a related but distinct safety problem: an intervention intended to be transient may leave a chromatin state whose duration, reversibility, genomic specificity, and phenotypic effects have to be established independently.

The central mechanistic question is therefore not simply whether an epigenetic editor can repress or activate a target. It is what happens after the initiating molecular intervention has ended. A useful theory must distinguish at least three temporal events: installation of a regulatory state while the editor is present, maintenance or modification of that state after withdrawal, and eventual persistence, erosion, or reversal of the transcriptional consequence. These events may be coupled, but they are not identical. The analysis that follows first establishes what can legitimately be called post-intervention persistence, then examines the chromatin-memory and feedback processes capable of stabilizing such a state. This provides the basis for a later account of why some edited states may become self-maintaining whereas others progressively lose regulatory control or remain durably but conditionally reversible.

Materials and Methods

Transient Epigenome Editing and the Problem of Regulatory Persistence

A rigorous claim of regulatory persistence requires a temporal separation between the editing intervention and the regulatory phenotype attributed to it. This separation has become experimentally accessible as delivery technologies move toward bounded exposure. Transient delivery of CRISPR epigenome-editor ribonucleoproteins has enabled repression through CRISPR interference, DNA-methylation editors and CRISPRoff-like systems, as well as TET1-based activation, without requiring prolonged production of the editing machinery. Durable silencing was observed across several human cellular settings after such delivery (Xu *et al.*, 2025). Primary human T-cell engineering provides a complementary case: transient RNA-based epigenetic programming can generate regulatory states that withstand proliferation and subsequent stimulation, demonstrating that disappearance of the initial editing reagent need not entail immediate restoration of the starting transcriptional state (Goudy *et al.*, 2026).

Persistence is not restricted to repression. At the imprinted Prader-Willi syndrome locus, transient targeted DNA demethylation of the normally silent maternal allele produced stable long-term activation in human induced pluripotent stem cells (Rohm *et al.*, 2025). The example is mechanistically informative because imprinting already contains specialized maintenance machinery; it therefore demonstrates what transient reprogramming can achieve in a favorable regulatory substrate without establishing that ordinary promoters will behave similarly. At the opposite end of the exposure spectrum, sustained repression obtained with viral delivery of compact CRISPR repressors illustrates an important interpretive control (Kantor *et al.*, 2024). When the delivery system itself can continue producing the effector, prolonged gene repression cannot by itself distinguish regulatory memory from prolonged molecular exposure. Demonstrating persistence consequently requires evidence about the intervention's disappearance as well as evidence about the target gene.

The installation phase also constrains what can persist. Targeted methylation with dCas9-DNMT3A-DNMT3L constructs can create promoter methylation and corresponding transcriptional repression (Stepper *et al.*, 2017). Alternative methyltransferase architectures, including engineered dCas9-MQ1, likewise demonstrate programmable deposition of cytosine methylation in vivo (Lei *et al.*, 2017). Split methyltransferase systems show that the extent and position of methylation can depend strongly on guide orientation and spatial relationship to the targeted sequence (Xiong *et al.*, 2017). Such results argue against treating an "epigenetic edit" as a uniform molecular entity. The initial state presented to the cell after editor withdrawal depends on where an effector acts, which modification is deposited or removed, how broadly that modification spreads, and how the edited region interacts with endogenous regulatory proteins.

Specificity creates a second problem. Genome-wide analysis of dCas9-methyltransferase activity has shown that engineered methylation systems can leave footprints extending beyond the intended local event, making global and local measurements necessary for interpreting apparent target-specific regulation (Galonska *et al.*, 2018). Regulatory topology can also alter the consequence of the same molecular operation. Targeting CTCF insulators with combinations of repressive and DNA-methylating effectors produced stable, partially heritable disruption in selected contexts, linking persistence to the architecture of a regulatory element rather than simply to promoter methylation (Tarjan *et al.*, 2019). Persistence should therefore be assigned to a defined molecular state at a defined regulatory unit, not to an editor platform in the abstract.

Reversibility further complicates classification. Targeted recruitment of TET1 together with factors that facilitate processing of oxidized methylcytosine can efficiently reduce DNA methylation and reactivate previously methylation-silenced genes (Taghbalout *et al.*, 2019). In neural progenitor cells, targeted removal of DNA methylation increased the fraction of cells able to respond to transcriptional reprogramming, showing that methylation can operate as an active barrier whose removal changes the accessibility of a regulatory transition (Baumann *et al.*, 2019). These interventions do not show that every methylation-supported state will decay spontaneously. They demonstrate that a regulatory state that persists after its installation can nevertheless contain identifiable molecular routes by which persistence is interrupted.

Taken together, the evidence supports a distinction between **bounded intervention**, **installed regulatory state**, and **post-intervention trajectory**. The first describes how long the editor remains functionally available. The second describes the chromatin and regulatory configuration produced while editing occurs. The third is the subsequent behavior of that configuration in the absence of the original intervention. Conflating these stages can make a long-lived delivery system appear to create memory, or make short-term repression appear to prove durable reprogramming. The scientific transition from transient editing to persistent regulation therefore requires evidence that the initiating editor has ceased to act and that the resulting chromatin-transcription relationship continues to be maintained.

The different experimental cases can be compared without assuming that they share one maintenance mechanism. **Table 1** organizes the observable states that must be distinguished before persistence is interpreted mechanistically.

Table 1. Post-intervention regulatory states that distinguish installed epigenetic change from continued editor action

Editing or regulatory context	State established during intervention	Critical evidence after intervention	Observed or plausible post-intervention behavior	Mechanistic interpretation permitted	Principal transfer boundary
Transient repressive epigenome editing	Local repressive chromatin and reduced transcription	Editor delivery is bounded; repression remains after exposure	Persistent silencing, partial erosion, or recovery	A chromatin state can outlast the initiating editor	Persistence remains locus-, effector-, and cell-dependent
Transient targeted DNA demethylation	Reduced promoter or regulatory-region methylation with transcriptional activation	Demethylase expression ends while activation continues	Stable activation or later remethylation	Removal of a maintenance mark can reset regulatory state	Imprinted loci may possess unusual maintenance logic
Targeted methyltransferase editing	Newly deposited CpG methylation	Local methylation and transcription measured separately from editor presence	Repression may persist only if methylation is subsequently maintained	Initial writing and subsequent maintenance are separate processes	Deposition efficiency does not establish memory
Hit-and-run insulator editing	Altered CTCF occupancy and local regulatory topology	Altered state persists after transient perturbation	Partially heritable disruption or restoration	Regulatory architecture can contribute to post-editing persistence	Effects depend on exact insulator and genomic context
Sustained vector-mediated repression	Repressor-associated chromatin with ongoing vector availability	Continued editor expression cannot be excluded	Long-duration repression	Supports therapeutic repression but not, by itself, autonomous memory	Exposure duration confounds persistence
Targeted active demethylation or barrier removal	Erasure of a repressive methylation barrier	Increased transcriptional responsiveness after erasure	Reactivation or increased state transition	Persistent repression can retain an experimentally accessible reversal route	Induced reversal is not evidence of spontaneous decay

The same distinction can be represented as a state landscape rather than a linear editing pipeline. After the editing pulse ends, regulatory behavior can remain near the installed state, drift toward the pre-intervention state, or move into a different stable configuration. Which trajectory is followed cannot be inferred from the identity of the editing tool alone. It depends on how the installed molecular state interacts with endogenous maintenance, transcription, replication and erasure processes.

Figure 1 summarizes regulatory-state trajectories after a transient epigenome-editing pulse.

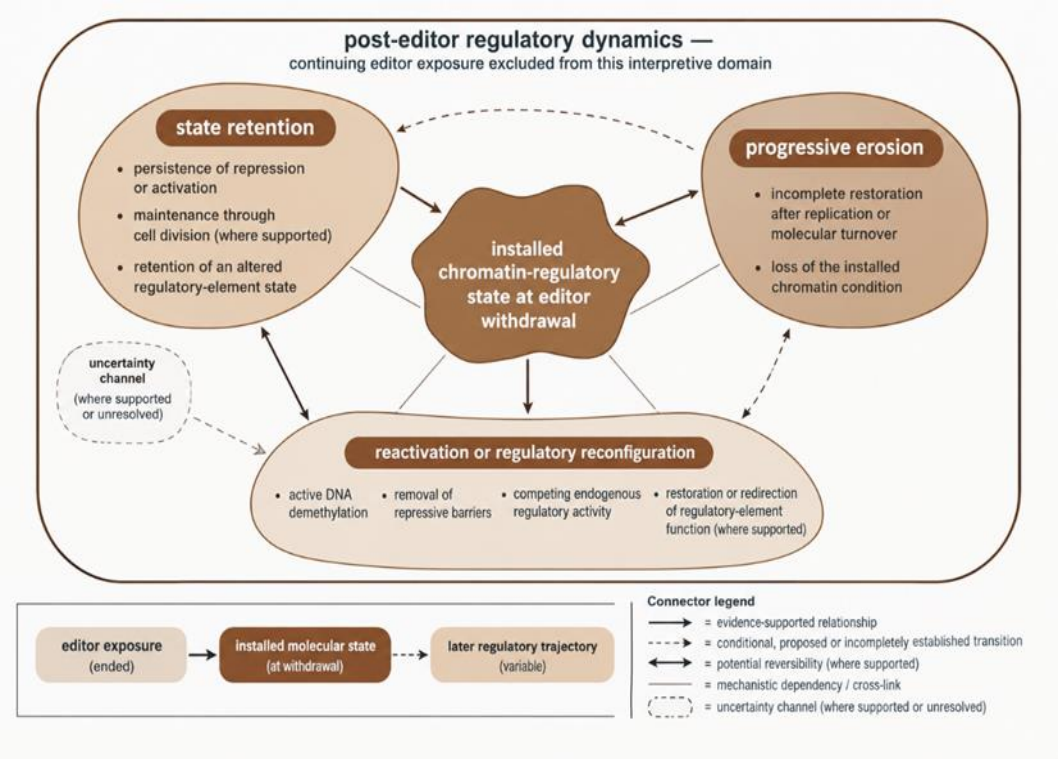


Figure 1. Regulatory-state trajectories after a transient epigenome-editing pulse

Chromatin Memory, Epigenetic Reinforcement, and Feedback Stabilization

Once editor exposure has ended, persistence requires some process capable of preserving or repeatedly reconstructing the regulatory state. Chromatin memory provides one route, but the term should not imply a single molecular substrate. Chromatin-associated regulation can stabilize cell identity through local feedback between regulatory activity and the molecular environment in which that activity occurs (Bell *et al.*, 2024). More generally, epigenetic transcriptional memory includes read-write processes through which cis-acting states at promoters or enhancers can be re-established and inherited, as well as forms of memory that alter the speed or probability of subsequent gene reactivation (Ge & Brickner, 2024). For therapeutic editing, the important implication is that the editor need not remain part of the maintenance machinery. Its role may instead be to move a locus into a configuration that endogenous cellular processes subsequently recognize and propagate.

DNA methylation offers the clearest conceptual example because maintenance machinery can reproduce methylation patterns after DNA replication at susceptible sites. Histone-associated memory is more heterogeneous. Mechanisms that propagate CpG methylation and H3K9 methylation demonstrate that some chromatin states possess molecular read-write logic capable of recreating a parental configuration, but the strength, fidelity and biological range of such inheritance differ among systems (Madhani, 2025). Experimental disruption of symmetric parental-histone inheritance in embryonic stem cells further shows that faithful transmission of modified histones contributes to preservation of the epigenomic landscape and appropriate cell-state transitions (Wenger *et al.*, 2023). These findings make replication a mechanistic stress test for persistence. A state that survives one cell cycle because an editor or modified molecule remains physically present is different from a state repeatedly reconstructed after dilution and chromatin assembly.

Self-maintenance also need not mean rigid chromatin immobilization. Polycomb repression illustrates the danger of assigning memory to an intuitively appealing physical structure without testing alternatives. Single-cell chromatin tracing of the *Hoxa* region showed that Polycomb-bound chromatin can explore relatively decompacted conformations while remaining transcriptionally repressed. Polymer modeling supported a spatial-feedback explanation in which transient contacts can contribute to propagation of the repressive state without requiring a permanently compact globular domain (Murphy & Boettiger, 2024). The broader implication is not that chromatin compaction is irrelevant at every locus. It is that sustained transcriptional repression can arise from dynamic interactions capable of regenerating regulatory conditions even when the underlying three-dimensional configurations fluctuate.

The relationship between feedback and memory may also be more graded than a simple division between “stable” and “unstable” states suggests. Targeted chromatin editing in an engineered human-cell system has demonstrated persistent intermediate expression states associated with different grades of DNA methylation, providing evidence for analog epigenetic memory (Palacios *et al.*, 2025). In that system, long-term expression could retain information about the magnitude of the preceding chromatin

perturbation rather than collapsing into only fully active or fully silent alternatives. Modeling further indicated that the organization of feedback among chromatin modifications influences whether such graded states can be retained. This result is especially important for therapeutic reasoning because it separates persistence from bistability. A locus can remember an intervention without necessarily becoming locked into one of two discrete transcriptional states.

These mechanisms suggest that "chromatin memory" is best treated as a functional property requiring mechanistic specification. After editor withdrawal, an installed state can persist because a modification is copied during replication, because reader-writer interactions restore a local chromatin environment, because regulatory proteins reinforce their own recruitment conditions, because three-dimensional contacts increase the probability of renewed repression, or because interacting transcriptional and chromatin processes stabilize a range of expression states. Different mechanisms may coexist at the same locus, and the mechanism that establishes a state need not be the mechanism that maintains it.

This distinction also clarifies why identical editing reagents need not generate identical durability across targets. The editor determines where and how a perturbation is initiated; the endogenous locus determines what happens afterward. CpG density, pre-existing chromatin, transcription-factor occupancy, regulatory topology, replication-associated restoration, cell identity and competing signaling inputs can all change whether an installed perturbation enters a self-reinforcing regime. Consequently, persistence should not be predicted solely from the presence of a nominally heritable mark such as DNA methylation. The relevant question is whether the surrounding molecular system contains sufficient maintenance logic to recreate the functionally important part of that state as its components turn over.

At the same time, self-reinforcement must not be equated with irreversibility. A chromatin state can be stable under ordinary cellular conditions yet remain susceptible to targeted demethylation, altered transcription-factor activity, changes in signaling, developmental transitions, or perturbation of the machinery that maintains it. The mechanistic problem therefore extends beyond identifying marks associated with durable repression. It requires explaining the balance between processes that reconstruct an edited state and processes that weaken, overwrite, or bypass it. That balance supplies the transition from descriptive evidence of chromatin memory to a theory of what should occur after therapeutic editor withdrawal—a theory that must account for durable maintenance, gradual erosion and reactivation without treating any one trajectory as inevitable.

A Mechanistic Theory of Persistence and Reversibility after Editor Withdrawal

The evidence supports a temporal account in which withdrawal of the editor is a mechanistic turning point rather than the end of the biological intervention. At that point, the locus is left in an altered regulatory condition whose future depends on whether endogenous processes can reproduce the functionally important features of that condition. Persistence is therefore best interpreted as continued reconstruction of a regulatory state after the initiating editor has ceased to act. The relevant contrast is not permanent versus temporary editing, but whether maintenance processes collectively outrun processes that dilute, erase, bypass, or replace the installed state.

This account allows prolonged stability to coexist with latent reversibility. Injury-induced chromatin memory in the mouse pancreas provides a useful mechanistic counterexample to the assumption that a durable chromatin state must be irreversible: inflammatory exposure can leave a state that changes subsequent cellular responses while remaining susceptible to pathway-dependent reversal (Falvo *et al.*, 2023). That system is not an epigenome-editing experiment and does not identify the pathway governing a therapeutically edited locus. Its value here is narrower. It demonstrates that molecular memory can remain biologically consequential after the initiating event yet still depend on conditions that can be experimentally disrupted. Duration and irreversibility are therefore separate properties.

The direction of regulatory change is also unlikely to be mechanistically symmetric. Bidirectional perturbation of transcriptional regulators has revealed hierarchical and interaction-dependent responses in which activation and repression do not behave as simple inverses (Pacalin *et al.*, 2025). In an edited chromatin context, establishing repression may require an initial writer or repressor, whereas reactivation may depend on demethylation, transcription-factor competition, replication-linked dilution, or disruption of maintenance feedback. A successful forward transition consequently does not imply that reversing the initiating perturbation will retrace the same molecular path. This directional asymmetry explains why an edited state may be readily established, persist for a period, and nevertheless require a qualitatively different perturbation to restore expression.

Recent primary-cell engineering further shows that durable epigenetic silencing can operate within complex therapeutic designs rather than only isolated reporter systems (Cipria *et al.*, 2026). Yet such success should not be converted into a universal durability rule. The theory developed here predicts three broad post-withdrawal trajectories without assigning fixed probabilities to them. Self-maintaining regulation occurs when endogenous reconstruction of the edited state remains sufficiently robust despite molecular turnover and, where relevant, cell division. Progressive loss occurs when restoration is incomplete, allowing the edited state and its transcriptional consequence to erode over time. Reversible reactivation occurs when competing regulatory processes or deliberate intervention move the locus out of the maintained state. Intermediate and graded trajectories remain possible, consistent with evidence that chromatin memory need not be binary.

A further implication is that trajectory assignment must remain locus-specific. Durable repression after transient hepatic editing provides unusually strong evidence because the regulatory phenotype persists after a regenerative challenge (Cappelluti *et al.*, 2024), but the same observation cannot specify which combination of DNA methylation, histone modification, transcriptional repression, or local regulatory architecture is indispensable at

another target. Mechanistic attribution therefore requires perturbing candidate maintenance processes rather than inferring them from duration alone. The theory deliberately permits more than one maintenance route to reach a similar long-lived phenotype.

The strongest evidence for self-maintenance would therefore combine verified editor clearance with longitudinal preservation of the relevant chromatin state and gene-regulatory phenotype. Evidence for progressive loss would require serial observation showing that the edited state weakens after withdrawal without renewed editing. Evidence for reversible reactivation would be stronger if a defined perturbation disrupted a maintenance process and restored expression while the original editor remained absent. These tests distinguish mechanistic persistence from a long endpoint measurement and turn the theory into an experimentally discriminating account.

The resulting boundaries are summarized in **Figure 2**. They represent conditions under which the same initial edited state can enter different post-withdrawal trajectories, not a deterministic sequence.

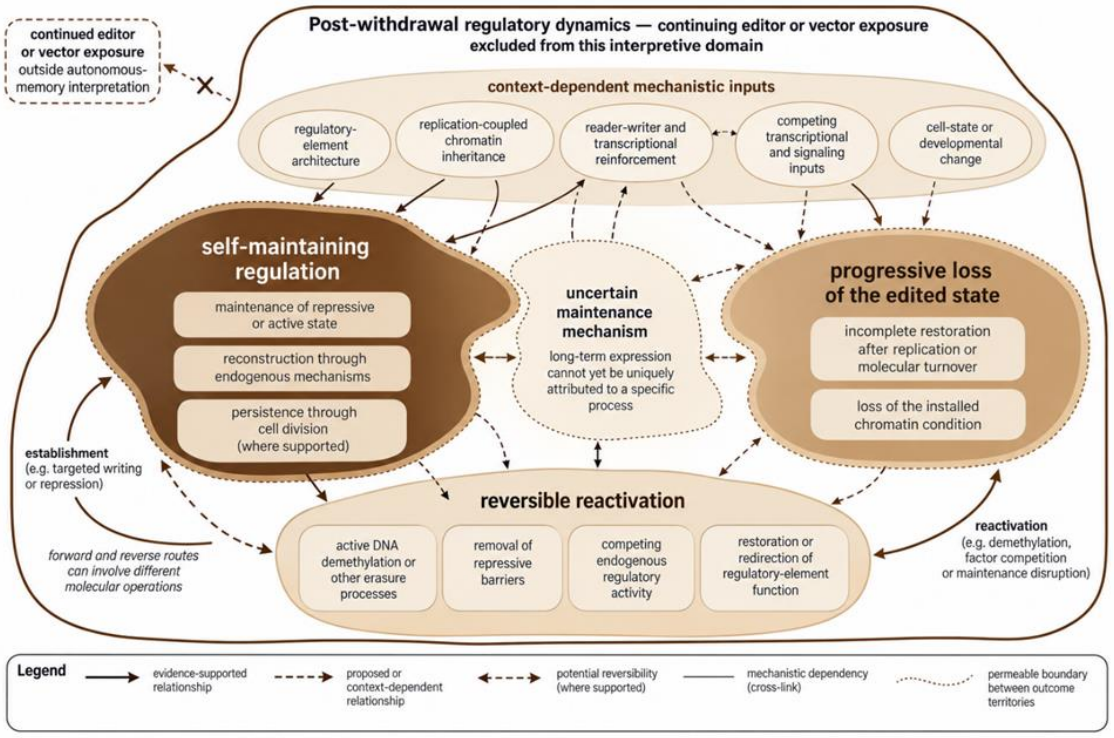


Figure 2. Mechanistic boundaries governing persistence, erosion, and reactivation after epigenome-editor withdrawal

Results and Discussion

Therapeutic Control, Durability, Safety, and Falsifiable Predictions

For therapeutic epigenome editing, durability is valuable only when it is coupled to specificity, appropriate functional effect, and a degree of reversibility suited to the clinical objective. Recent translational assessments identify loss of an intended epigenetic modification, unintended editing, incomplete functional coupling, delivery constraints, and uncertain duration among the central obstacles to therapeutic development (Choi *et al.*, 2026; Yuan *et al.*, 2026). A durable molecular mark is therefore not itself a successful therapy. The relevant endpoint is durable and appropriate regulation in the intended cell population without unacceptable effects elsewhere.

This distinction changes how persistence should be validated. A persuasive study should establish when editor activity has ended, then follow the target chromatin state and transcriptional output across biologically meaningful intervals. Transient RNP delivery provides one route for creating a bounded exposure (Xu *et al.*, 2025), whereas longitudinal targeted-editing studies show why later expression states must be resolved rather than reduced to a single terminal measurement (Palacios *et al.*, 2025). Where cell division is expected, replication becomes an informative perturbation because persistence must survive dilution and chromatin reassembly. Where the target tissue is largely non-dividing, molecular turnover and competing regulatory signals become more informative tests.

The theory also generates falsifiable predictions. A claim of autonomous chromatin memory would be weakened if apparent durability disappeared once residual editor activity was excluded. A proposed maintenance mechanism would be weakened if its selective disruption left persistence unchanged. Conversely, persistence after verified clearance, survival through proliferative challenge, and predictable loss after disruption of a maintenance process would support a self-reinforcing interpretation. Reactivation produced through a mechanistically distinct route

would support directional asymmetry between establishment and reversal.

This approach also avoids imposing an arbitrary temporal threshold for "durable" editing. Clinically meaningful duration depends on tissue turnover, disease course, intended treatment interval, and the consequences of unintended persistence. A post-withdrawal trajectory is more informative than a universal time cutoff because it asks whether regulation is stable, changing, or recoverable under conditions relevant to the target tissue. It also creates a direct connection between mechanistic experiments and therapeutic control: the same perturbations used to identify maintenance processes can reveal possible escape or rescue routes if the edited state later becomes undesirable.

Safety requires the same mechanistic resolution. Avoiding sequence alteration does not eliminate the need to investigate unintended molecular consequences (Fiumara *et al.*, 2024). Genome-wide footprints produced by targeted methylation systems show that local on-target measurements alone are insufficient for judging specificity (Galonska *et al.*, 2018). A second safety problem is excessive durability: a regulatory intervention that cannot be readily reversed may become undesirable if physiology, disease state, or therapeutic goals change. Designing for controllable persistence may therefore be more useful than maximizing durability without qualification.

The practical implication is that therapeutic epigenome editing should be optimized for a defined post-withdrawal trajectory. Some indications may require durable repression through many cell divisions; others may favor a state that persists long enough to produce benefit but remains accessible to reversal. Mechanistic characterization of maintenance and escape routes can make this property testable rather than treating durability as a descriptive afterthought.

Conclusion

Transient epigenome editing can generate gene-regulatory effects that outlast the molecular intervention, but persistence should not be treated as an intrinsic property of an epigenetic mark or editing platform. The evidence instead supports a conditional process in which an installed regulatory state encounters endogenous mechanisms that may reconstruct it, gradually fail to maintain it, or permit its reversal. Chromatin inheritance, local feedback, regulatory topology, molecular turnover, competing transcriptional programs, and cell state can therefore determine whether a transient intervention becomes durable regulation.

The central theoretical implication is that persistence and reversibility belong to the same post-withdrawal trajectory. A state may be stable without being irreversible, and successful establishment need not imply that reactivation follows the reverse molecular route. Therapeutic evaluation should consequently establish editor clearance, follow chromatin and transcription longitudinally, and perturb candidate maintenance mechanisms where feasible. Such evidence would distinguish genuine regulatory memory from prolonged exposure and would allow durability to be designed together with specificity, function, and controllability rather than pursued as an isolated endpoint.

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