

PERSPECTIVE ARTICLE

Temporal genomic memory: A testable systems biology framework linking metabolic–epigenetic coupling to cancer initiation

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Abstract

Cancer initiation has traditionally been explained by the progressive accumulation of somatic genetic alterations. Although this paradigm remains fundamental, increasing evidence indicates that long-term biological exposures including chronic inflammation, metabolic dysfunction, oxidative stress, mitochondrial adaptation, and immune dysregulation can produce persistent regulatory changes that are not fully explained by DNA sequence variation alone. Existing concepts such as epigenetic memory, metabolic memory, trained immunity, and adaptive cellular plasticity each describe important aspects of biological persistence but do not provide an integrated framework explaining how prolonged exposure histories may influence future oncogenic susceptibility. Here, we propose temporal genomic memory (TGM) as a testable systems biology framework describing how sustained biological experiences may be progressively integrated, compressed, and retained as persistent regulatory states through coordinated interactions among metabolic signaling, mitochondrial function, chromatin remodeling, regulatory RNA networks, and tissue-level immune adaptation. Unlike existing memory paradigms that primarily emphasize individual regulatory mechanisms, the proposed framework introduces regulatory compression as a conceptual process through which diverse biological signals are consolidated into latent molecular configurations capable of influencing future transcriptional responsiveness. Under permissive conditions such as aging, chronic inflammation, immune decline, or recurrent metabolic stress, these latent regulatory states may undergo molecular recall, thereby modifying cellular responses to subsequent biological challenges and potentially increasing oncogenic susceptibility in cooperation with established genetic and environmental factors. A conceptual mathematical representation is introduced to describe biological signal accumulation, regulatory compression, and recall activation while emphasizing its heuristic rather than predictive purpose. We further propose experimentally testable strategies based on chronic exposure, stress-withdrawal persistence, recall-challenge paradigms, and integrated multi-omics analyses to evaluate the hypothesis. Temporal genomic memory is not intended to replace the somatic mutation theory of cancer. Instead, it provides a complementary systems-level perspective integrating metabolic history, mitochondrial signaling, epigenetic regulation, and persistent

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Citation: Aziz SSA, Kassem KF, Salah MS. Temporal genomic memory: A testable systems biology framework linking metabolic–epigenetic coupling to cancer initiation. *Innov Med Omics*. doi: 10.36922/IMO026210026

Received: May 20, 2026

Revised: July 26, 2026

Accepted: August 20, 2026

Published online: August 28, 2026

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transcriptional adaptation into a unified theoretical framework for investigating long-latency cancer initiation.

Keywords: Temporal genomic memory; Cancer initiation; Epigenetic memory; Mitochondrial signaling; Regulatory compression; Molecular recall; Systems biology; Oncogenic susceptibility

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide despite substantial advances in molecular oncology, precision medicine, and cancer genomics.¹ For more than four decades, the somatic mutation theory has provided the dominant conceptual framework for understanding cancer initiation and progression by attributing malignant transformation primarily to the gradual accumulation of genetic alterations that confer selective growth and survival advantages. Extensive genomic studies have confirmed the central importance of driver mutations, chromosomal instability, and clonal evolution in tumor development, firmly establishing mutation-centered models as a foundation of modern cancer biology.²⁻⁴ Nevertheless, increasing evidence indicates that malignant transformation cannot always be explained solely by irreversible alterations in DNA sequence. The marked variability in cancer latency, tissue susceptibility, and disease risk despite apparently comparable mutational backgrounds suggests that non-genetic regulatory mechanisms may also influence cancer initiation and evolution.⁵

In parallel with advances in cancer genomics, growing attention has been directed toward the contribution of non-genetic mechanisms to long-term cellular adaptation. Epigenetic regulation—including DNA methylation, histone modifications, chromatin remodeling, and higher-order chromatin organization—provides dynamic yet potentially persistent control over gene expression without altering the underlying nucleotide sequence.⁶⁻⁹ These regulatory mechanisms respond to intracellular metabolism, inflammatory signaling, oxidative stress, aging, environmental exposure, endocrine regulation, and tissue-specific microenvironmental conditions. Importantly, epigenetic alterations may persist after disappearance of the initiating stimulus, thereby creating durable regulatory states capable of influencing future cellular behavior.⁹⁻¹²

The concept of biological memory has consequently emerged across several disciplines. Epigenetic memory describes the persistence of chromatin-associated

regulatory states following transient environmental or developmental stimulation. Metabolic memory refers to the prolonged consequences of previous metabolic disturbances, particularly persistent hyperglycemia, even after restoration of glycemic control.¹³ Trained immunity demonstrates that innate immune cells can undergo long-lasting functional reprogramming following microbial or inflammatory stimulation, resulting in altered responses to subsequent challenges.¹⁴ Adaptive cellular plasticity similarly describes the ability of differentiated cells to undergo sustained phenotypic remodeling in response to environmental pressure. Collectively, these observations demonstrate that cells can retain biologically meaningful consequences of previous exposures.

Although these concepts have advanced understanding of long-term biological adaptation, each principally addresses a specific regulatory dimension. Epigenetic memory focuses predominantly on chromatin-associated mechanisms; metabolic memory emphasizes the persistent consequences of metabolic disturbance; trained immunity concerns functional reprogramming of innate immune cells; and cellular plasticity describes sustained changes in cellular identity or function. None independently provides an integrated explanation of how diverse biological experiences accumulated over prolonged periods may collectively modify future oncogenic susceptibility. An important conceptual gap therefore remains concerning how prolonged biological history may be represented within living cells and subsequently influence responses to oncogenic challenges.

Cancer initiation is particularly suitable for examining this question because clinically detectable malignancy may emerge only after prolonged exposure to chronic inflammation, metabolic dysfunction, oxidative injury, mitochondrial stress, immune dysregulation, environmental factors, or repeated tissue damage. During this extended latency period, cells continuously integrate signals derived from nutrient availability, mitochondrial activity, reactive oxygen species, inflammatory mediators, endocrine signaling, extracellular matrix remodeling, and immune surveillance. The mechanisms through

which these cumulative experiences might persist, and later influence cellular susceptibility remain incompletely understood.

Recent advances have further demonstrated the close relationship between metabolism and gene regulation. Metabolites including acetyl-coenzyme A, α -ketoglutarate, succinate, fumarate, nicotinamide adenine dinucleotide, and S-adenosylmethionine function as substrates, cofactors, or regulators of chromatin-modifying enzymes and transcriptional programs.^{10-12,15} Mitochondria therefore operate not only as bioenergetic organelles but also as signaling hubs coordinating metabolism, redox regulation, inflammatory responses, and nuclear gene expression.¹⁵⁻¹⁷ Persistent metabolic conditions may consequently reshape regulatory architecture over prolonged periods without requiring permanent alteration of genomic DNA.

Building on these observations, we propose temporal genomic memory (TGM) as a complementary systems biology framework rather than a replacement for established paradigms. TGM integrates epigenetic regulation, metabolic adaptation, mitochondrial signaling, inflammatory biology, regulatory RNA networks, and tissue-level responses into a unified temporal framework. Unlike models that primarily describe individual mechanisms of biological persistence, TGM introduces regulatory compression, whereby prolonged and diverse biological experiences are progressively integrated into latent regulatory configurations that retain the cumulative influence of previous exposures rather than preserving each event independently.

These latent configurations are hypothesized to remain biologically silent or functionally restrained until permissive physiological conditions induce their preferential reactivation through molecular recall. Such recall may modify subsequent transcriptional responsiveness and influence susceptibility to oncogenic transformation. Regulatory compression and molecular recall are therefore proposed as higher-order organizational principles rather than newly discovered molecular pathways.

The proposed framework does not suggest that persistent regulatory conditioning independently causes cancer, nor does it challenge the importance of somatic mutations in malignant transformation. Instead, TGM proposes that prolonged biological history may modify the probability with which subsequent genetic, metabolic, inflammatory, or environmental events promote malignant progression. Genetic alterations remain essential determinants of cancer development, whereas persistent regulatory conditioning may influence the biological context in which these alterations exert their effects.

The objective of this Perspective is to present a testable conceptual framework integrating prolonged biological exposure, metabolic–epigenetic coupling, mitochondrial signaling, regulatory compression, and molecular recall into a unified hypothesis for investigating long-latency cancer initiation. We further propose experimentally accessible strategies to determine whether regulatory states generated by chronic biological stress persist after stress withdrawal and whether their subsequent reactivation modifies cellular responses to oncogenic challenges.

2. Conceptual framework and literature approach

This Perspective introduces temporal genomic memory (TGM) as a hypothesis-generating systems biology framework developed through conceptual integration rather than the discovery of a single molecular mechanism. The framework synthesizes evidence from cancer genomics, epigenetics, mitochondrial biology, metabolic regulation, systems biology, trained immunity, cellular plasticity, and chronic inflammation to explain how prolonged biological experiences may collectively influence future oncogenic susceptibility.¹⁸⁻²⁴

Unlike existing models that primarily address individual regulatory processes, TGM proposes that sustained biological exposures are progressively integrated into stable latent regulatory configurations through a process termed regulatory compression. Rather than preserving each biological event independently, repeated metabolic, inflammatory, mitochondrial, epigenetic, and transcriptional signals are proposed to converge into systems-level regulatory states that retain the cumulative influence of prior exposures while reducing molecular complexity.

TGM should not be considered synonymous with epigenetic memory, metabolic memory, trained immunity, or adaptive cellular plasticity.^{7,11,12,14,21-24} Instead, these mechanisms are viewed as complementary manifestations of a broader temporal regulatory process integrating biological history across multiple interconnected systems. Within this framework, TGM represents the cumulative encoding of prolonged biological exposure through coordinated interactions among metabolic, mitochondrial, epigenetic, inflammatory, transcriptional, and tissue regulatory networks, generating latent configurations capable of modifying future cellular responses after appropriate biological triggers.

The framework also complements, rather than replaces, the somatic mutation theory. While mutation-centered models explain cancer through progressive

genetic alterations and clonal evolution²⁻⁴, TGM proposes that prolonged regulatory conditioning modifies the biological context in which these mutations arise and exert their effects. Persistent regulatory memory is therefore considered an additional temporal layer influencing oncogenic susceptibility rather than an alternative mechanism of carcinogenesis (Figure 1).

Because this article presents a theoretical framework rather than experimental evidence, the mathematical model is intended as a heuristic conceptual representation rather than a predictive algorithm. Likewise, the proposed experimental strategy establishes explicit criteria by which the hypothesis can be supported, refined, or rejected. Failure to detect persistent regulatory states after chronic exposure, or to demonstrate altered recall responses following secondary challenges, would argue against the proposed framework. Accordingly, TGM should be regarded as an experimentally testable conceptual synthesis designed to guide future investigation into the temporal dimension of cancer initiation.

3. Temporal biological information encoding

Living cells continuously integrate metabolic, inflammatory, endocrine, microbial, mechanical, and environmental signals. While most responses are transient, prolonged biological stress can induce persistent regulatory adaptations that outlast the initiating stimulus. Although DNA methylation, histone modifications, chromatin accessibility, regulatory RNA networks, mitochondrial signaling, metabolic reprogramming, and immune adaptation each contribute to long-term cellular memory, they are generally studied independently and do not fully explain how decades of biological experience influence future cellular behavior.^{7-18,21-28}

The TGM framework proposes that repeated or sustained biological stimuli are progressively integrated into stable regulatory configurations rather than preserved as individual molecular events. In this model, biological history is represented by cumulative regulatory

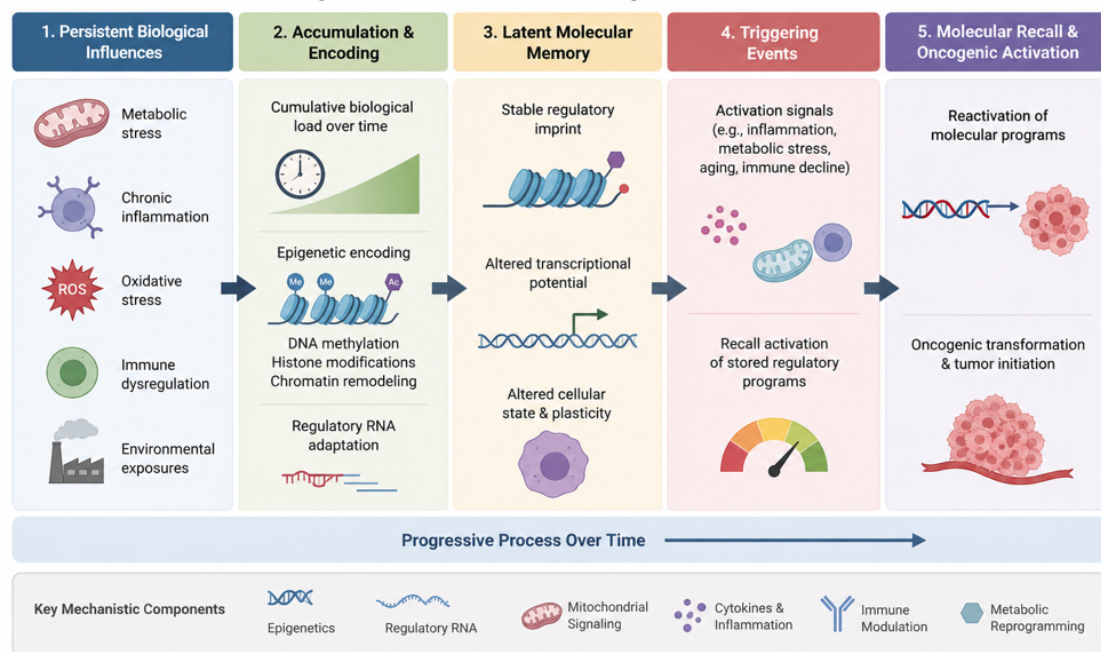


Figure 1. Integrated systems model of temporal genomic memory in cancer initiation. Prolonged biological pressures, including chronic inflammation, metabolic dysfunction, oxidative stress, mitochondrial adaptation, immune dysregulation, environmental exposure, and tissue injury, generate continuous biological signal accumulation. These signals undergo progressive temporal biological information encoding and regulatory compression, producing latent systems-level regulatory configurations that may persist following removal of the initiating stimulus. Under secondary biological challenges such as aging, chronic inflammation, immune decline, recurrent metabolic stress, or hypoxia, molecular recall preferentially reactivates previously conditioned regulatory architecture, thereby modifying transcriptional responsiveness and cellular adaptation. Rather than replacing the somatic mutation paradigm, the proposed framework introduces a complementary temporal-regulatory layer that may influence the biological context in which established oncogenic mechanisms operate. Figure created by the authors using BioRender.com and Adobe Illustrator (Adobe Inc., San Jose, CA, USA).

architecture whose formation depends on the intensity, duration, recurrence, and interaction of biological signals. Rather than functioning as a literal molecular archive, these regulatory states summarize prolonged biological experience while remaining dynamic and continuously modified by ongoing physiological conditions.

A defining feature of this framework is regulatory compression, whereby heterogeneous biological inputs including metabolic activity, mitochondrial signaling, inflammation, chromatin remodeling, transcription factor dynamics, and regulatory RNA networks are consolidated into coordinated latent regulatory configurations. Unlike conventional epigenetic memory, which emphasizes persistence of individual molecular marks^{7–12,21–24}, regulatory compression represents a systems-level organization of integrated biological history. Because these configurations arise from dynamic network interactions rather than permanent molecular fixation, they retain the capacity for both persistence and gradual remodeling over time.

An important consequence of temporal biological information encoding is that previously established regulatory configurations may influence future transcriptional responsiveness, stress adaptation, mitochondrial function, inflammatory behavior, and tissue repair long after the initiating stimulus has disappeared. TGM therefore proposes two complementary stages of long-term adaptation: temporal encoding, during which biological experiences are progressively integrated, and regulatory compression, through which these experiences become stabilized as latent regulatory configurations capable of influencing subsequent cellular responses.

Although regulatory compression has not yet been demonstrated directly, observations from epigenetics, mitochondrial biology, metabolic regulation, trained immunity, systems biology, and integrated multi-omics are consistent with the existence of persistent adaptive regulatory states.^{11–18,21–28} Within the TGM framework, these findings are interpreted as components of a broader temporal process that generates experimentally testable predictions regarding persistence, reversibility, and context-dependent molecular recall.

4. The biological capsule model: A conceptual representation of long-term regulatory integration

The biological capsule model illustrates how prolonged biological experience may be integrated into persistent regulatory states without requiring storage of every individual molecular event. Rather than functioning

as a physical cellular structure, the model serves as a conceptual representation of long-term information integration. Continuous biological exposures including metabolic activity, inflammation, mitochondrial function, endocrine signaling, immune surveillance, tissue repair, environmental factors, and aging are proposed to undergo progressive regulatory compression, yielding latent regulatory configurations that preserve cumulative biological influence while minimizing molecular complexity.^{15,16,18,21–28}

These compressed configurations remain biologically relevant after removal of the initiating stimulus and may alter future cellular responses when challenged by aging, chronic inflammation, metabolic stress, hypoxia, immune decline, or mitochondrial dysfunction through a process termed molecular recall. Within this perspective, mutations and regulatory memory act as complementary determinants of carcinogenesis operating across different temporal dimensions.

The biological capsule model also generates explicit experimental predictions. If prolonged biological conditioning produces persistent regulatory states, previously exposed cells should retain stable multi-layer regulatory signatures after stress withdrawal and exhibit altered responses to standardized secondary challenges compared with biologically naïve controls. Failure to demonstrate these features would argue against the proposed framework. Thus, the model serves as a conceptual bridge linking prolonged biological exposure with experimentally testable mechanisms of delayed oncogenic susceptibility.

5. Mitochondrial signaling and energy-driven regulatory conditioning

Mitochondria function not only as the primary source of cellular energy but also as central regulators of metabolism, redox homeostasis, apoptosis, inflammation, and nuclear gene expression.^{15–18,22,23,25,28} Because mitochondrial activity responds continuously to nutrient availability, inflammatory signaling, oxidative stress, hypoxia, aging, and environmental exposures, it provides an important interface linking prolonged biological experience with long-term regulatory adaptation.^{15,16,22,23,25}

Within the TGM framework, mitochondria are proposed to facilitate regulatory conditioning by coupling metabolic activity to epigenetic regulation. Metabolites such as acetyl-coenzyme A, α -ketoglutarate, succinate, fumarate, nicotinamide adenine dinucleotide (NAD⁺), flavin adenine dinucleotide (FAD), and S-adenosylmethionine regulate chromatin-modifying enzymes, thereby connecting persistent metabolic

states with transcriptional remodeling without altering DNA sequence.^{9,10,18,21–25} Sustained metabolic epigenetic interactions may therefore contribute to the gradual formation of stable regulatory configurations.

Importantly, mitochondria are not proposed to store biological memory. Instead, they act as dynamic signaling hubs that continuously translate prolonged metabolic and environmental conditions into coordinated adaptations involving chromatin remodeling, regulatory RNA expression, inflammatory signaling, and transcriptional regulation.^{15,16,22,23,25,28} Repeated metabolic or inflammatory stress may progressively reinforce these adaptive networks, contributing to the regulatory compression proposed by the TGM framework.

Unlike conventional models that focus primarily on mitochondrial dysfunction after disease develops, TGM emphasizes prolonged mitochondrial adaptation as a conditioning process that precedes pathological transformation. This Perspective offers a mechanistic link between chronic metabolic disorders, persistent inflammation, and delayed cancer susceptibility while remaining fully compatible with mutation-driven models of oncogenesis.^{15,22,25,28}

The framework generates clear experimental predictions. Cells exposed to chronic metabolic stress should retain persistent mitochondrial-associated regulatory changes after stress withdrawal and exhibit altered chromatin organization, transcriptional responses, and metabolic behavior following secondary challenges. Failure to detect such persistent conditioning would argue against this component of the model. Thus, mitochondria are viewed as systems-level integrators that connect long-term metabolic history with regulatory adaptation preceding cancer initiation.

6. Regulatory compression and molecular recall: The defining features of temporal genomic memory

The principal innovation of the TGM framework is the proposal that long-term biological adaptation involves not only persistent molecular modifications but also the progressive organization of diverse biological information into stable regulatory configurations. This process, termed regulatory compression, distinguishes TGM from existing concepts of epigenetic memory, metabolic memory, and trained immunity.

Current models describe persistence primarily through individual mechanisms such as DNA methylation, histone modification, mitochondrial adaptation, transcription factor activity, immune reprogramming, and metabolic–

epigenetic coupling.^{7–18,21–28} TGM proposes that prolonged biological experiences are progressively integrated across these interconnected networks, producing latent regulatory configurations that represent cumulative biological history rather than isolated molecular events.

These latent configurations remain relatively stable through coordinated interactions among chromatin organization, mitochondrial metabolism, regulatory RNA networks, inflammatory signaling, and transcriptional regulation.^{8–18,21–28} Their persistence reflects systems-level network stability rather than permanent fixation of individual molecular marks, allowing continued adaptation as new biological experiences accumulate.

The second defining component of the framework is molecular recall, which describes the preferential reactivation of previously conditioned regulatory configurations following secondary biological challenges such as chronic inflammation, recurrent metabolic stress, oxidative injury, hypoxia, immune decline, mitochondrial dysfunction, endocrine imbalance, microbial stimulation, or aging. Rather than retrieving stored molecular information, molecular recall represents context-dependent reactivation of latent regulatory architecture, resulting in altered transcriptional responses compared with biologically naïve cells.

Because regulatory conditioning modifies response probability rather than determining outcome, molecular recall should be viewed as a probabilistic systems-level phenomenon. Cellular responses therefore depend on previous biological history together with tissue context, genetic background, and current physiological conditions, providing a potential explanation for variability in cancer susceptibility and disease latency among individuals with similar environmental exposures.

Together, regulatory compression and molecular recall establish a temporal layer of biological regulation linking prolonged exposure history with future cellular behavior. Rather than replacing established models of carcinogenesis, these concepts propose that persistent regulatory conditioning modifies the biological context in which recognized oncogenic mechanisms operate.

Importantly, the framework is experimentally testable. Regulatory compression predicts persistent multi-layer regulatory signatures following prolonged biological exposure, whereas molecular recall predicts altered responses to standardized secondary challenges after stress withdrawal. Failure to demonstrate either persistent regulatory configurations or preferential recall responses would provide evidence against the proposed model. These experimentally falsifiable predictions distinguish TGM from a purely descriptive conceptual framework.

7. Conceptual mathematical representation of temporal genomic memory

The mathematical framework presented below is intended exclusively as a conceptual systems biology representation designed to facilitate scientific discussion and guide future experimental investigation. It should not be interpreted as a predictive computational model, a validated quantitative algorithm, or a formal mathematical description of cellular behavior. Instead, the equations provide an abstract representation of the proposed relationships among prolonged biological exposure, regulatory integration, latent persistence, and molecular recall within the TGM framework.

The following mathematical structure is not intended as a validated predictive equation. Rather, it provides a heuristic model that conceptually links exposure duration, metabolic intensity, regulatory compression, and molecular recall, thereby offering a framework for designing experimentally testable hypotheses.

(A) Accumulation of biological signal

$$M(T) = \text{integral from } 0 \text{ to } T \text{ of } I(t) \times E(t) \, dt$$

where $I(t)$ represents cumulative biological signaling at time t , including metabolic, inflammatory, oxidative, endocrine, microbial, and immune inputs^{10–18,21–28}; $E(t)$ represents the cellular metabolic and regulatory capacity determined by mitochondrial function and energy-dependent adaptation^{9,10,15–18,21–25}; T denotes the duration of biological exposure; and $M(T)$ represents the cumulative regulatory conditioning generated during prolonged biological adaptation.

(B) Information compression

$$C = f(M, K)$$

where C denotes the compressed regulatory configuration; and K represents a biological compression coefficient reflecting chromatin plasticity, tissue context, metabolic adaptability, and the capacity of cells to stabilize integrated regulatory information.^{8–10,18,21–24}

(C) Molecular recall activation

$$R = g(C, T_r)$$

where R represents the level of molecular recall activation; and T_r represents secondary biological triggers including aging, immune decline, chronic inflammation, oxidative stress, hypoxia, or metabolic imbalance.^{11–18,21–28}

(D) Oncogenic transition threshold

$$R > \theta$$

where θ represents a conceptual threshold beyond which

persistent regulatory conditioning may contribute to increased oncogenic susceptibility. This threshold does not imply that regulatory conditioning alone is sufficient to initiate malignant transformation. Rather, it proposes that persistent regulatory states may cooperate with somatic mutations, tissue injury, immune dysfunction, and environmental stressors to increase the probability of pathological cellular reprogramming, consistent with current models of multistep carcinogenesis.^{2–4,15,16}

8. Integrated systems model of cancer initiation

Cancer initiation has traditionally been explained by the progressive accumulation of somatic mutations followed by clonal selection and evolutionary expansion.^{2–4} Although this mutation-centered paradigm remains the foundation of modern oncology, the TGM framework proposes that prolonged regulatory conditioning may modify the biological context in which genetic alterations arise and exert their functional effects.

Within this framework, cancer initiation is viewed as a multi-layer process involving coordinated interactions among genetic, metabolic, epigenetic, mitochondrial, inflammatory, immune, and environmental regulatory systems.^{3,7–18,21–28} While acute biological stimuli generally induce reversible adaptive responses, persistent biological pressures including chronic inflammation, metabolic dysfunction, oxidative stress, endocrine imbalance, microbial exposure, repeated tissue injury, and aging may progressively remodel regulatory architecture through temporal biological information encoding and regulatory compression.^{10–18,21–28}

The proposed model consists of four sequential stages: (i) biological signal accumulation, during which cells continuously integrate metabolic, inflammatory, mitochondrial, and environmental information; (ii) regulatory compression, whereby prolonged biological experiences are consolidated into stable latent regulatory configurations; (iii) latent persistence, in which these configurations remain biologically stable despite apparent restoration of homeostasis; and (iv) molecular recall, where subsequent physiological or pathological triggers reactivate conditioned regulatory programs, thereby modifying future cellular responses.

Importantly, these regulatory processes are proposed to modify oncogenic susceptibility rather than independently initiate malignant transformation. Persistent regulatory conditioning may influence how subsequent oncogenic events, including somatic mutations, chromosomal instability, immune escape, or microenvironmental remodeling, promote malignant progression. Thus, TGM

complements rather than replaces mutation-driven models of carcinogenesis.^{2–4,15,16,25}

The framework also provides a potential explanation for the marked variability in cancer latency and tissue susceptibility observed among individuals with similar environmental exposures or comparable mutational burdens.^{3,5,15,21,25,26} Differences in accumulated regulatory history may partially account for these variations by altering the adaptive landscape in which genetic alterations occur. Likewise, prolonged regulatory conditioning may remain clinically silent for years before physiological transitions such as aging, immune decline, recurrent inflammation, or renewed metabolic stress trigger molecular recall and increase oncogenic susceptibility.

Importantly, TGM remains fully compatible with current concepts of clonal evolution and cancer systems biology by introducing an upstream temporal-regulatory layer rather than an alternative mechanism of carcinogenesis.^{2–5,26} Because the framework is conceptual, its validity depends on experimental demonstration that prolonged biological conditioning produces persistent regulatory states and altered responses following standardized recall challenges. Failure to observe these features would require revision of the proposed model.

9. Proposed experimental validation strategy

A major strength of the TGM framework is that it generates explicit, experimentally falsifiable predictions. Rather than seeking to confirm the hypothesis, the proposed validation strategy aims to determine whether prolonged biological exposure induces persistent regulatory conditioning that remains detectable after stress withdrawal and modifies cellular responses to subsequent biological challenges.

9.1. Phase I: Establishment of persistent regulatory conditioning

Human-derived cellular models relevant to metabolism-associated malignancies, including HepG2 hepatocytes, primary hepatocytes, intestinal organoids, pancreatic β -cell models, mammary epithelial cells, and colonic epithelial cell lines, may be exposed to chronic metabolic or inflammatory stress. Experimental stimuli may include sustained hyperglycemia, elevated free fatty acids, inflammatory cytokines, oxidative stress, intermittent hypoxia, mitochondrial inhibitors, or microbial-associated molecular patterns. Following prolonged exposure, all stimuli should be withdrawn, and cells maintained under physiological conditions. Persistence of regulatory alterations during this recovery period would provide the first indication of long-term regulatory conditioning.

9.2. Phase II: Multi-omics characterization

Persistent regulatory states should be evaluated using integrated molecular profiling, including whole-genome DNA methylation analysis, histone modification profiling (ChIP-seq), chromatin accessibility analysis (ATAC-seq), bulk and single-cell RNA sequencing, regulatory non-coding RNA sequencing, spatial transcriptomics (when appropriate), untargeted metabolomics, and mitochondrial functional assays.

Rather than focusing on individual biomarkers, integrated systems-level analysis should determine whether prolonged conditioning generates coordinated regulatory architectures consistent with the proposed concept of regulatory compression.

9.3. Phase III: Molecular recall challenge

Following recovery, previously conditioned cells and untreated controls should receive identical secondary biological challenges, including inflammatory cytokines, oxidative stress, hypoxia, glucose re-exposure, lipid overload, Toll-like receptor agonists, DNA damage, or oncogenic pathway activation. The central prediction is that previously conditioned cells will display altered transcriptional, metabolic, mitochondrial, or inflammatory responses despite identical experimental conditions, consistent with molecular recall.

9.4. Systems-level data integration

Because TGM involves coordinated regulation across multiple biological layers, multi-omics datasets should be integrated using systems biology approaches such as gene regulatory network analysis, multi-omics factor analysis, Bayesian inference, weighted gene co-expression network analysis, machine learning, dynamic trajectory analysis, and causal network modeling. These analyses may identify persistent regulatory configurations associated with prior biological conditioning.

9.5. *In vivo* validation

Animal models of chronic metabolic or inflammatory disease, including obesity, diabetes, inflammatory bowel disease, non-alcoholic steatohepatitis, chronic infection, or repeated tissue injury, may be used to determine whether prolonged biological conditioning influences subsequent cancer susceptibility after recovery and carcinogenic challenge. Longitudinal studies could further evaluate the evolution and stability of regulatory conditioning during aging.

10. Implications for cancer initiation

If experimentally validated, TGM would suggest that cancer initiation is influenced not only by genetic mutations but

also by long-term regulatory history. Chronic metabolic disease, persistent inflammation, oxidative injury, immune dysfunction, and environmental exposure may create a permissive epigenetic background in which later oncogenic events are more likely to generate malignant behavior.

This Perspective may help explain why cancer can emerge after long latency periods and why tissues exposed to chronic injury may remain biologically altered even after partial clinical recovery. It may also support preventive strategies aimed at reversing pathological regulatory memory before irreversible transformation occurs.

11. Conclusion

Cancer initiation is widely recognized as a complex, multi-stage biological process driven by interactions among genetic, epigenetic, metabolic, inflammatory, and environmental factors.^{2-5,7-18,21-28} Although the somatic mutation theory remains the cornerstone of modern oncology, increasing evidence indicates that prolonged biological exposures can generate persistent regulatory alterations that are not fully explained by irreversible DNA sequence changes alone.^{5,7-18,21-28} These observations have stimulated growing interest in understanding how long-term biological experience may influence future cellular behavior.

In this Perspective, we propose temporal genomic memory (TGM) as a testable systems biology framework that integrates concepts from metabolism, mitochondrial biology, epigenetics, inflammation, regulatory RNA biology, and adaptive cellular regulation into a unified temporal model of cancer susceptibility. Rather than viewing persistent biological adaptation as isolated molecular events, the framework introduces regulatory compression as a conceptual mechanism through which prolonged biological experiences may be progressively integrated into latent regulatory configurations. Subsequent molecular recall is proposed to represent the preferential reactivation of these previously conditioned regulatory states under appropriate biological conditions.

Importantly, the framework is not intended to replace the somatic mutation theory or other established models of oncogenesis. Instead, it provides a complementary temporal-regulatory perspective suggesting that prolonged biological history may influence the regulatory environment in which recognized oncogenic mechanisms operate. Within this interpretation, genetic mutations remain essential drivers of malignant transformation, whereas persistent regulatory conditioning may contribute to variability in cancer latency, tissue susceptibility, and adaptive cellular responses.^{2-5,15,16,25,26}

A major strength of the proposed framework is its experimental accessibility. By generating explicit and falsifiable predictions regarding persistent regulatory conditioning, regulatory compression, and molecular recall, the hypothesis provides a practical foundation for future investigation using contemporary experimental approaches, including multi-omics profiling, single-cell technologies, spatial transcriptomics, systems biology, and longitudinal disease models.²¹⁻²⁸ The framework therefore encourages direct experimental testing rather than conceptual acceptance.

The authors recognize that the present model remains hypothesis-generating and that its defining concepts have not yet been experimentally validated. Whether regulatory compression represents a distinct systems-level biological phenomenon, or an emergent property of previously recognized adaptive mechanisms can only be determined through future investigation. Consequently, the principal contribution of this Perspective is not the establishment of a new biological theory but the formulation of a coherent conceptual framework capable of generating experimentally testable questions regarding the temporal dimension of cancer initiation.

If future studies demonstrate that prolonged biological exposure generates persistent, integrated regulatory configurations capable of influencing subsequent cellular responses, the TGM framework may provide a useful systems-level perspective for understanding long-latency disease development. Conversely, if such regulatory conditioning cannot be demonstrated experimentally, the framework should be refined or rejected accordingly. In either outcome, systematic evaluation of the hypothesis is expected to advance understanding of the relationship between biological history, regulatory adaptation, and cancer initiation.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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Writing–original draft: All authors

Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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