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Review Article

When Cells Remember Stress: A Multilayer Framework Linking Transient Adaptation to Persistent Cellular Reprogramming

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ABSTRACT

Cells are continuously exposed to fluctuations in redox state, nutrient availability, oxygen tension, proteotoxic burden, inflammation, and other forms of stress. Most acute stress responses are reversible, yet a subset of stress-induced changes persists after the initiating stimulus has disappeared and alters how cells respond to subsequent challenges. This review develops a conceptual framework termed “multilayer stress memory,” used here as a descriptive framework rather than as an established biological entity. The framework proposes that persistent stress responses arise from coordinated changes across interconnected molecular layers, including the epigenome, transcriptome, metabolome, mitochondria, RNA-regulatory networks, proteome, and proteostasis machinery. These layers do not operate independently: metabolic intermediates influence chromatin, mitochondrial state affects redox signaling, proteostatic stress reshapes translation and transcription, and inflammatory or hypoxic signaling can stabilize cellular states. The resulting memory may be adaptive, maintaining enhanced resilience, or maladaptive, maintaining inflammatory, oxidative, metabolic, or survival programs that contribute to chronic disease and therapeutic resistance. We distinguish molecular memory, functional memory, and pathological memory and discuss experimental strategies capable of testing persistence rather than merely detecting stress-induced molecular changes. Finally, we consider whether maladaptive memory can be selectively reprogrammed without eliminating beneficial stress adaptation.

Keywords: cellular stress; stress memory; epigenetics; metabolic memory; mitochondrial memory; proteostasis; transcriptional reprogramming; redox signaling; cellular adaptation; therapeutic reprogramming

INTRODUCTION

Cells constantly adjust to changes in their environment by modifying gene expression, metabolic activity, protein synthesis, and organelle function. These responses help cells cope with challenges and restore homeostasis when conditions return to normal. However, recovery is not always a complete return to the original cellular state. In some circumstances, the effects of an earlier exposure persist even after the initiating stimulus has disappeared, influencing how cells respond to subsequent challenges. This phenomenon is reflected in several established research areas, including metabolic memory, epigenetic memory, and trained immunity, in which previous exposures can leave lasting molecular or functional consequences (Tonna et al., 2010; Kato and Natarajan, 2019; Netea et al., 2020).

Although these phenomena share the idea that previous experiences can shape future cellular behaviour, they are often investigated within separate research fields. Studies of epigenetic memory focus on persistent changes in chromatin structure and gene regulation, whereas metabolic memory examines the long-term consequences of earlier metabolic conditions. In innate immunity, trained immunity describes changes in cellular responsiveness associated with metabolic and epigenetic reprogramming. Mitochondrial stress responses and protein-quality-control systems add further dimensions by linking organelle function, energy metabolism, and the maintenance of protein integrity to cellular adaptation (Kato and Natarajan, 2019; Netea et al., 2020; Dai et al., 2020; Eisner et al., 2018). These perspectives are complementary rather than interchangeable, and together they suggest that persistent cellular changes may arise through several interconnected mechanisms rather than through a single universal pathway.

To bring these observations together, we propose the term multilayer stress memory to describe a persistent cellular state that develops after stress exposure and alters the response to a later challenge through interactions among transcriptional, epigenetic, metabolic, mitochondrial, RNA-regulatory, and proteostatic processes. The central idea is that these mechanisms should not be considered isolated components. For example, metabolic changes can influence chromatin-modifying reactions, while epigenetic regulation can sustain altered gene-expression patterns; in trained immunity, metabolic and epigenetic reprogramming can jointly support changes in cellular function. Such interactions provide a plausible basis for persistent cellular states, although their relative contributions will depend on the cell type, stressor, and biological context (Dai et al., 2020; Netea et al., 2020; Dong et al., 2024). Importantly, *multilayer stress memory* is proposed here as a conceptual framework, not as an established biological term or a universally demonstrated mechanism.

A useful way to examine this framework is to distinguish between molecular memory, functional memory, and pathological memory. Molecular memory refers to the mechanisms that maintain the consequences of an earlier exposure, such as persistent epigenetic modifications or changes in regulatory networks. Functional memory describes the altered cellular behaviour that remains after the initial stimulus has been removed, including a modified response to a subsequent challenge. Pathological memory represents a more specific outcome in which these persistent changes contribute to disease, for example when previous metabolic disturbances continue to influence inflammatory or tissue-damaging processes despite improvement in the original conditions. These distinctions are intended to clarify different levels of analysis, rather than to establish three formally recognized biological categories (Kato and Natarajan, 2019; Netea et al., 2020; Dong et al., 2024).

The critical question, therefore, is not simply whether a stressor changes the expression of a gene or the abundance of a molecular marker. It is whether the resulting changes persist after the stress has been withdrawn and whether they can be linked to a measurable alteration in the cell's response to a later challenge. This distinction is particularly important when attempting to separate a genuine memory-like phenomenon from a prolonged response to an ongoing stimulus. Establishing cellular memory consequently requires evidence of persistence, an appropriate assessment of the post-stress state, and, where possible, a second challenge that reveals the functional consequences of the earlier exposure. Research on metabolic memory and trained immunity provides relevant examples of why both the persistence of molecular changes and their functional significance matter (Tonna et al., 2010; Netea et al., 2020; Natarajan, 2024).

Viewed in this way, cellular stress memory can be represented as a sequence: stress → encoding → persistence → memory → second challenge → adaptation or maladaptation. This sequence is a conceptual model rather than a universal, strictly linear biological pathway. Its value lies in highlighting the transition from an acute response to a lasting state and, ultimately, to a potentially beneficial or harmful outcome. The translational challenge is to determine whether maladaptive forms of cellular memory can be selectively reversed while preserving the protective mechanisms that enable cells to survive and adapt to future stress. Addressing this question may help identify therapeutic strategies that target persistent disease-associated cellular states rather than only the immediate pathways activated during stress (Netea et al., 2020; Dong et al., 2024). This conceptual transition from acute response to persistent memory and subsequent challenge response is illustrated in Figure 1.

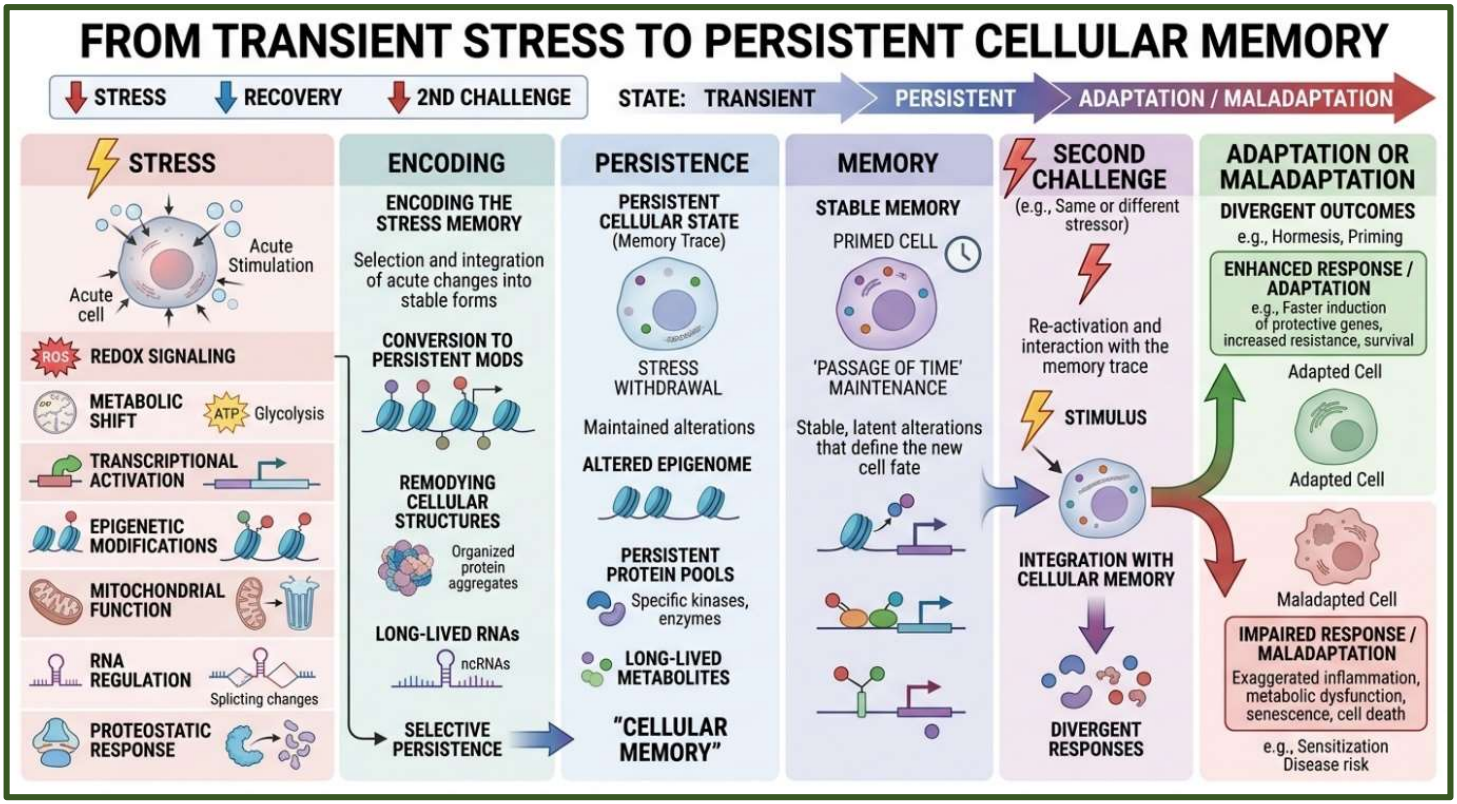


Figure 1. Sequential framework of cellular stress memory. Acute stress induces transient multi-layered responses. Under specific regimes, select changes undergo encoding and persistence following stimulus withdrawal, forming a latent memory trace. Exposure to a secondary challenge engages this memory, driving divergent outcomes toward adaptive priming or maladaptive pathology.

2. Encoding Stress: Molecular Layers That Convert Transient Signals into Persistent States

2.1 Epigenetic encoding

Chromatin is a plausible mechanism through which the effects of cellular stress can persist beyond the initial exposure. Changes in histone modifications, DNA methylation, nucleosome organization, and chromatin accessibility can influence how readily genes are activated or repressed, potentially allowing stress-induced transcriptional patterns to persist after the original stimulus has been removed. These processes are closely connected to cellular metabolism. Metabolites such as acetyl-CoA and S-adenosylmethionine provide substrates for histone acetylation and methylation, respectively, while α-ketoglutarate and NAD^+ support the activity of enzymes involved in chromatin regulation. Consequently, stress-induced metabolic changes can influence chromatin states, which may, in turn, reinforce or modify subsequent patterns of gene expression. This reciprocal relationship provides a mechanistic basis for understanding how temporary environmental changes may produce longer-lasting transcriptional effects (Kaelin and McKnight, 2013; Reid et al., 2017; Kato and Natarajan, 2019).

Metabolic memory in diabetic complications offers a well-studied example of this phenomenon. Experimental studies have shown that transient exposure to high glucose can induce persistent changes in gene expression and epigenetic regulation, including alterations associated with inflammatory and vascular dysfunction, even after glucose levels return to normal. For example, El-Osta et al. (2008) demonstrated that prior hyperglycemia could sustain activating histone modifications at the *RELA* promoter, contributing to persistent expression of the proinflammatory factor NF-κB p65 in vascular cells. Such findings support the idea that the biological consequences of an earlier metabolic disturbance may outlast the disturbance itself. However, the presence of an epigenetic modification alone does not establish cellular memory. A stronger demonstration requires evidence that the change persists after the initiating stimulus has been withdrawn and contributes to a measurable functional effect. This distinction is essential when evaluating whether chromatin changes represent a genuine mechanism of stress memory or simply a residual molecular response (El-Osta et al., 2008; Brasacchio et al., 2009; Kato and Natarajan, 2019).

2.2 Transcriptional encoding

Stress-responsive transcription factors, including NRF2, hypoxia-inducible factors (HIFs), ATF4, FOXO proteins, and NF-κB, help cells adapt to changes in their environment by coordinating the expression of genes involved in antioxidant defence, metabolism, inflammation, and survival. Although these responses are often

initiated rapidly, their consequences may extend beyond the period of stress exposure. Depending on the cellular context, repeated stimulation or sustained pathway activation can reshape transcriptional activity and alter how cells respond to subsequent challenges. Several mechanisms may contribute to this persistence, including self-reinforcing regulatory networks, sustained enhancer activity, changes in chromatin accessibility, and feedback loops that maintain altered patterns of gene expression. Research on enhancer-mediated transcriptional memory and stress-responsive regulatory networks supports the possibility that previous cellular experiences can influence later transcriptional responses (D'Urso et al., 2016; Sood et al., 2010; Netea et al., 2020).

From this perspective, transcriptional memory is better understood as a property of interconnected regulatory networks than as the continued activity of a single transcription factor. NRF2, for example, regulates antioxidant and cytoprotective genes, whereas NF-κB coordinates many inflammatory responses; both operate within broader networks influenced by chromatin state, upstream signalling, and cellular metabolism. However, persistent expression of their target genes does not necessarily establish transcriptional memory, because ongoing signalling or incomplete recovery may produce similar effects. Demonstrating genuine memory therefore requires showing that altered transcription persists after the initiating stimulus has been removed and, ideally, that it changes the response to a subsequent challenge. This distinction provides a useful framework for investigating how initially protective stress responses may become durable adaptations or contribute to maladaptive cellular states (D'Urso et al., 2016; Kato and Natarajan, 2019; Netea et al., 2020).

2.3 Metabolic encoding

Cellular metabolism does more than provide the energy and building blocks required for survival; it also influences how cells sense stress, regulate gene expression, and adapt to changing conditions. Changes in glycolysis, lipid metabolism, amino-acid utilization, or the tricarboxylic acid (TCA) cycle can affect the availability of metabolites that participate in signalling and chromatin regulation. Similarly, shifts in the NAD^+/NADH ratio and cellular redox balance can influence enzyme activity, mitochondrial function, and stress-responsive pathways. Because these processes are closely interconnected, an initial stressor may leave metabolic changes that influence cellular responses even after the original conditions have improved. Such interactions provide a mechanistic basis for metabolic persistence, although the specific pathways involved are likely to differ across cell types and stress conditions (Kaelin and McKnight, 2013; Reid et al., 2017; Chandel, 2021).

However, a persistent change in metabolite abundance does not, by itself, establish metabolic memory. Metabolite levels may fluctuate with nutrient availability, ongoing signalling, or incomplete recovery from the initial insult. A stronger case for metabolic memory requires evidence that the altered metabolic state remains after the initiating stress has been removed and contributes to a measurable change in cellular behaviour or responsiveness to a subsequent challenge. Metabolic memory in diabetes illustrates this distinction, as earlier hyperglycemia can have lasting biological consequences despite subsequent glucose normalization. Combining metabolic measurements with functional experiments and, where appropriate, analysis of the regulatory mechanisms maintaining the altered state would therefore provide a more convincing basis for identifying genuine metabolic memory (El-Osta et al., 2008; Kato and Natarajan, 2019).

2.4 Mitochondrial encoding

Mitochondria play a central role in cellular stress responses, extending beyond their well-known function in energy production. They help regulate redox signaling, calcium homeostasis, apoptosis, and the availability of metabolic intermediates that influence nuclear gene expression. In response to stress, mitochondrial structure and function may change, including alterations in morphology, respiratory activity, membrane potential, reactive oxygen species (ROS) production, and mitochondrial quality-control mechanisms such as mitophagy. Although many of these changes are reversible, some may persist after the initial stress has subsided, potentially influencing how cells respond to subsequent challenges. Mitochondria may therefore contribute to cellular stress memory by maintaining changes in metabolic and redox signaling that continue to affect nuclear regulatory pathways (Chandel, 2015; Picard et al., 2016).

The possibility of mitochondrial stress memory is particularly relevant when altered mitochondrial function persists and continues to influence cellular behavior. For example, sustained changes in ROS production or mitochondrial metabolism may affect stress-responsive transcriptional pathways, while impaired mitochondrial quality control may allow dysfunctional organelles to accumulate. These processes could help maintain an altered cellular state even after the original stressor has been removed. However, persistent mitochondrial dysfunction should not automatically be interpreted as memory. A convincing demonstration requires evidence that mitochondrial changes remain after stress withdrawal and contribute to a lasting functional alteration, ideally including a modified response to a subsequent challenge. This distinction places mitochondrial persistence within the broader framework of cellular stress memory without assuming that all long-lasting mitochondrial

changes represent a distinct memory mechanism (Youle and van der Bliek, 2012; Picard et al., 2016; Chandel, 2021).

2.5 RNA-mediated persistence

RNA regulation provides another way for cells to retain the effects of previous stress exposure. MicroRNAs, long non-coding RNAs, and circular RNAs can influence gene expression at different stages, from RNA processing and stability to translation. Stress can also alter alternative splicing, changing which transcript variants are produced and, consequently, which proteins are available to support cellular adaptation. Although many of these changes are initially part of a short-term protective response, some may persist after the original stress has subsided, particularly when RNA stability or regulatory feedback mechanisms sustain altered patterns of gene expression. Non-coding RNAs can also connect different regulatory systems by interacting with chromatin-modifying proteins, metabolic pathways, mitochondrial functions, and inflammatory signaling. In this way, RNA-mediated regulation may contribute to the persistence of stress-induced cellular changes and influence how cells respond to subsequent challenges, although its role in establishing long-term cellular memory depends on the specific RNA, cell type, and stress context (Sadek et al., 2019; Verduci et al., 2019; Scholda et al., 2024).

Rather than operating as isolated linear pathways, these individual layers form an integrated, multidirectional network Figure 2.

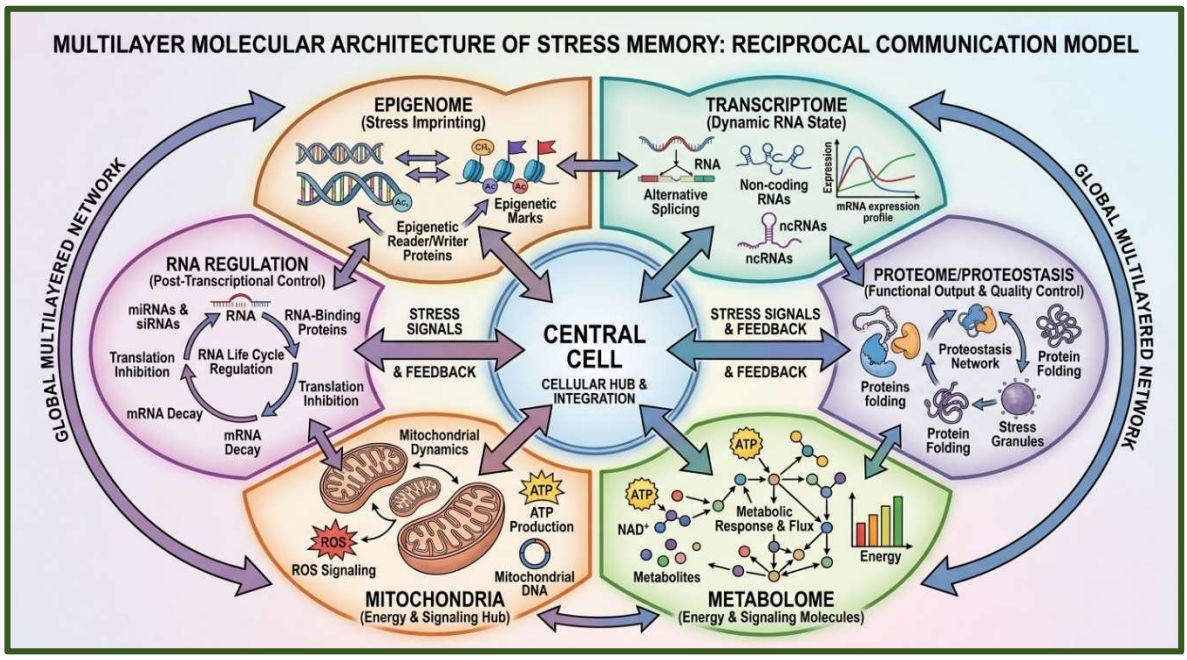


Figure 2. Multilayer molecular architecture of stress memory. Reciprocal network model of cellular memory maintenance. Stress memory emerges from systemic crosstalk across six interconnected modules: epigenome, transcriptome, proteome/proteostasis, metabolome, mitochondria, and post-transcriptional RNA regulation. Bidirectional feedback loops ensure the persistence and propagation of the memory state across cellular recovery phases.

3. The Stress-Memory Network: Integration of Redox, Proteostatic, Metabolic, and Hypoxic Signaling

3.1 NRF2–KEAP1 signaling

The NRF2–KEAP1 pathway provides a useful example of how cells adapt to stress, although NRF2 itself should not be considered a molecular memory store. Under normal conditions, KEAP1 helps maintain low NRF2 levels by directing it for ubiquitination and proteasomal degradation. When cells encounter oxidative or electrophilic stress, modifications to KEAP1 can weaken this control, allowing NRF2 to accumulate, enter the nucleus, and activate genes involved in antioxidant defense, detoxification, and cellular protection (Yamamoto et al., 2018; Yamamoto et al., 2023). This response helps cells cope with an immediate challenge, but its activation alone does not establish that a memory of stress has been formed. Longer-lasting changes may emerge when repeated stress or interactions with epigenetic regulation, metabolic pathways, mitochondrial function, and protein quality-control systems sustain an altered cellular state. NRF2 is therefore best understood as part of a wider regulatory network that coordinates stress adaptation, while the persistence of that adaptation depends on the mechanisms that maintain cellular changes after the initial stimulus has disappeared (Hayes and Dinkova-Kostova, 2014; Zhang, 2025).

3.2 Integrated stress response

The integrated stress response (ISR) allows cells to adjust their activity when faced with different forms of stress, including amino-acid deprivation, oxidative damage, and the accumulation of misfolded proteins. Although triggered by different stress-sensing kinases, these signals converge on the phosphorylation of eukaryotic initiation factor 2α (eIF2α), which reduces general protein synthesis while promoting the translation of ATF4 and the activation of downstream stress-responsive genes. Through this mechanism, the ISR helps coordinate amino-acid metabolism, redox homeostasis, autophagy, and decisions about cell survival (Pakos-Zebrucka et al., 2016; Costa-Mattioli and Walter, 2020). When stress is repeated or prolonged, changes in the regulation of this pathway may influence how effectively cells respond to subsequent challenges. However, whether such changes constitute persistent cellular stress memory depends on their duration and on whether altered responsiveness remains after the original stress has been removed.

3.3 Unfolded protein response and proteostasis

The unfolded protein response (UPR) helps cells cope with stress in the endoplasmic reticulum (ER), particularly when newly synthesized proteins accumulate in an unfolded or misfolded state. This response is coordinated mainly by three signaling pathways involving PERK, IRE1, and ATF6, which work together to restore ER function by adjusting protein synthesis, increasing the expression of molecular chaperones, and promoting the removal of misfolded proteins. The UPR also influences lipid metabolism, autophagy, and other processes that help maintain cellular homeostasis (Walter and Ron, 2011; Hetz et al., 2020). When these responses persist or alter the capacity of the cell to manage subsequent disturbances in protein folding, they may influence how the cell responds to later stress. In this sense, lasting changes in proteostasis—the balance between protein synthesis, folding, and degradation—could contribute to cellular stress memory, although this interpretation requires evidence that the altered state remains after the original stress has subsided.

3.4 AMPK–mTOR signaling

AMPK and mTOR act as key regulators of how cells balance energy supply with their demands for growth, repair, and survival. When energy becomes limited, AMPK helps cells conserve resources by restraining energy-intensive processes and promoting pathways that generate ATP. In contrast, mTOR integrates signals from nutrients, growth factors, and cellular energy status to regulate protein synthesis, biosynthesis, and autophagy. The interplay between these pathways allows cells to adjust their priorities according to changing metabolic conditions (Saxton and Sabatini, 2017; Herzig and Shaw, 2018). If these adjustments persist after an energetic challenge has passed, they may influence how cells respond to later stress. AMPK–mTOR signaling can also link metabolic adaptation with proteostasis by coordinating energy availability with protein synthesis and degradation. Such persistent changes could contribute to cellular stress memory, although demonstrating this requires evidence that the altered regulatory state outlasts the initial stress.

3.5 HIF signaling

Hypoxia-inducible factors (HIFs) help cells adapt when oxygen availability falls. By regulating genes involved in glycolysis, angiogenesis, mitochondrial metabolism, and cell survival, HIF signaling allows cells to adjust their energy production and maintain essential functions under low-oxygen conditions (Semenza, 2012; Choudhry and Harris, 2018). When hypoxia occurs repeatedly, or when metabolic changes mimic aspects of oxygen deprivation, the resulting responses may extend beyond the immediate challenge. Alterations in gene expression and metabolic activity may persist and influence how cells respond to subsequent episodes of stress. However, sustained HIF activity alone does not establish hypoxic memory. To demonstrate such memory, it is necessary to show that changes in cellular state remain after oxygen levels return to normal and that these changes modify the response to a later challenge.

3.6 Autophagy and proteostasis

Autophagy and proteostasis determine how efficiently damaged proteins and organelles are removed. Stress-induced changes in autophagic capacity can influence subsequent stress tolerance because autophagy is both an effector and regulator of metabolism and organelle quality.

Together, these intersecting signaling networks demonstrate that cellular stress memory is inherently distributed across multiple structural and functional tiers rather than localized to a single molecular switch. The interplay among redox balance, proteostasis, metabolic fluxes, organellar dynamics, and post-transcriptional regulators ensures that an initial stress signal can be encoded, maintained, and propagated across cellular divisions or extended post-stimulus windows. To provide a systematic synthesis of these interconnected systems, Table 1 outlines the primary molecular layers contributing to cellular stress memory, detailing their representative mechanisms, key regulators, persistent maintenance modes, functional consequences, and prospective therapeutic intervention nodes.

Table 1. Molecular layers contributing to stress memory

Molecular layer	Representative mechanisms	Key regulators	Persistence mechanism	Potential consequence	Therapeutic opportunity
Epigenetic	DNA methylation; histone modifications; chromatin accessibility	DNMTs; TETs; HATs/HDACs	Stable regulatory chromatin states	Persistent gene-expression programs	Targeted epigenome editing
Transcriptional	TF activation; enhancer remodeling; feedback loops	NRF2; HIFs; ATF4; NF-κB; FOXO	Network stabilization	Altered baseline stress responsiveness	Targeted signaling/TF modulation
Metabolic	Glycolysis; TCA; lipid/amino-acid metabolism	AMPK; mTOR; metabolic enzymes	Persistent flux and metabolite signaling	Metabolic dysfunction or resilience	Metabolic pathway modulation
Mitochondrial	Respiration; ROS; membrane potential; mitophagy	PGC-1α; quality-control pathways	Persistent organelle remodeling	Altered energy/redox state	Mitochondrial quality-control interventions
RNA	miRNAs; lncRNAs; RNA stability; translation	RNA-binding proteins; miRNA machinery	Persistent RNA-regulatory networks	Durable post-transcriptional control	RNA-targeted therapeutics
Proteostatic	UPR; chaperones; autophagy; ERAD	PERK; IRE1; ATF6; HSF1	Altered proteostasis capacity	Changed proteotoxic tolerance	Proteostasis/autophagy modulation
Inflammatory/immune	Cytokine signaling; innate immune training	NF-κB; inflammasomes	Stable functional reprogramming	Enhanced defense or chronic inflammation	Context-specific immunomodulation

4. From Adaptive Memory to Maladaptive Memory: Determinants of Cellular Fate

The long-term consequences of stress are not always harmful. In some cases, exposure to a mild stressor prepares cells to cope more effectively with a later challenge, whereas severe or prolonged stress can sustain inflammatory, oxidative, or metabolic changes that eventually become detrimental. These contrasting outcomes suggest that cellular stress memory depends not only on the initial stimulus but also on how strongly the cell responds, how long the response lasts, and the biological context in which it occurs. Factors such as age, metabolic status, mitochondrial function, epigenetic regulation, previous stress exposure, and genetic background may all influence whether the resulting changes promote resilience or contribute to disease.

Building on this idea, we propose a conceptual *stress-memory threshold model* to explain how different levels of stress burden may lead to distinct cellular outcomes. At relatively low levels of stress, cellular responses are generally transient and subside once homeostasis is restored. At an intermediate level, some changes may persist and improve the response to a subsequent challenge, producing adaptive stress memory. However, when stress is sufficiently intense or prolonged, compensatory responses may

become sustained or dysregulated, reinforcing processes such as chronic inflammation, metabolic dysfunction, or abnormal cell survival. These categories are intended to represent a continuum rather than fixed biological thresholds, since the transition between adaptation and maladaptation is likely to vary across cell types and physiological conditions.

The consequences of a stress response also depend on the pathway involved and the context in which it remains active. NRF2-mediated antioxidant signaling, for example, can protect cells against acute oxidative injury, yet persistent NRF2 activity may support tumor-cell survival and treatment resistance in certain cancers. Similarly, trained immunity can enhance protection against subsequent infections but may also contribute to chronic inflammatory disorders when immune reprogramming becomes maladaptive. Together, these examples illustrate why pathway activation alone is insufficient to define cellular stress memory. What matters is whether the resulting changes persist, how they interact with other regulatory systems, and whether their lasting effects improve the ability to withstand future challenges or instead promote disease (Calabrese and Mattson, 2017; Rojo de la Vega et al., 2018; Netea et al., 2020). The transition between transient adaptation, beneficial priming, and pathological persistence across stress intensity and duration is mapped in the stress-memory threshold model Figure 3.

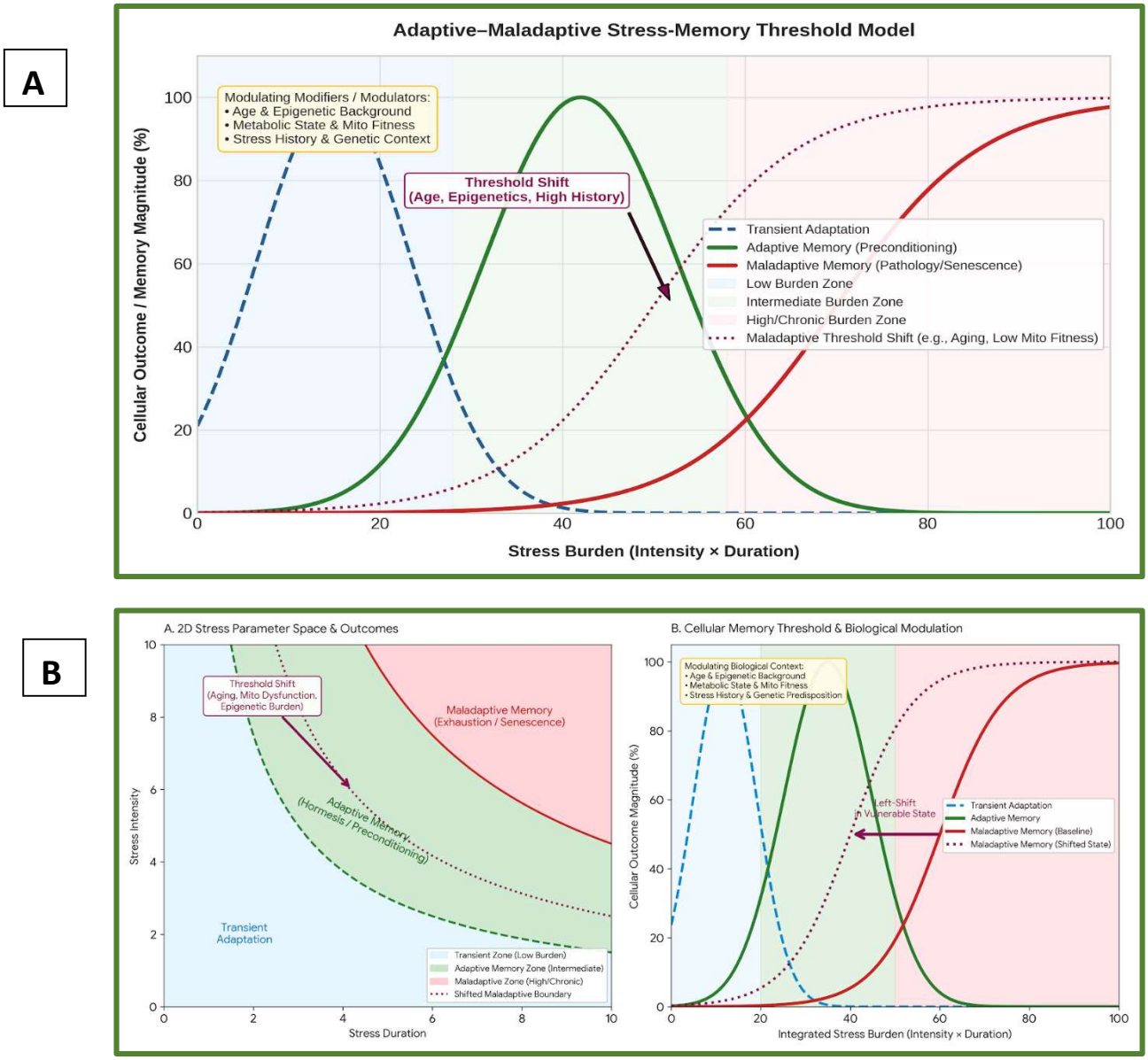


Figure 3. Adaptive–maladaptive stress-memory threshold model. (A) Stress parameter phase space. (B) Integrated outcome dynamics.

5. Experimental Strategies to Identify and Test Stress Memory

A central methodological challenge is separating stress persistence from stress memory. Detecting an altered marker immediately after stress demonstrates a response, not memory. Strong evidence requires a recovery period sufficient to remove the initiating stimulus, demonstration that a molecular or functional state persists, and ideally a second challenge showing altered responsiveness.

ATAC-seq, ChIP-seq, CUT&RUN, and CUT&Tag can characterize chromatin accessibility and regulatory marks, while RNA-seq, single-cell RNA-seq, and spatial transcriptomics can identify persistent transcriptional states and cellular heterogeneity. Metabolomics and stable-isotope tracing can determine whether metabolic flux remains altered rather than merely showing changed metabolite abundance. Mitochondrial respiration, membrane potential, morphology, ROS production, and mitophagy assays can test organelle-level persistence. Live-cell imaging can reveal recovery trajectories.

CRISPR-based epigenome editing can move beyond correlation by selectively modifying regulatory elements or chromatin states. Perturb-seq and related single-cell perturbational approaches can connect molecular interventions with phenotypic consequences. Multi-omics integration may identify coupled states across layers, but statistical correlation does not by itself establish causality. Strong designs combine temporal sampling, stress withdrawal, second-challenge experiments, causal perturbation, and functional readouts.

6. Can Stress Memory Be Reprogrammed?

If maladaptive cellular stress memory is sustained by interactions between several molecular systems, treating the resulting dysfunction may require more than simply suppressing the stress response. A more selective approach would aim to identify and disrupt the mechanisms that keep the pathological state active while preserving pathways that support normal adaptation. Potential therapeutic targets include epigenetic regulators, metabolic signaling pathways, redox homeostasis, mitochondrial quality control, autophagy, proteostasis, and upstream signaling proteins that coordinate these processes (Dong et al., 2024; Sies and Jones, 2020).

Epigenetic mechanisms may be particularly relevant when persistent changes in chromatin help maintain abnormal patterns of gene expression. However, broadly inhibiting chromatin-modifying enzymes could disrupt normal gene regulation and erase beneficial adaptations alongside pathological ones. Metabolic interventions present a similar challenge because pathways that sustain disease in one context may be essential for cellular survival in another (Dong et al., 2024). Redox-directed therapies also require careful consideration: reactive oxygen species can cause molecular damage when produced excessively, but they also act as signaling intermediates that help coordinate physiological adaptation (Sies and Jones, 2020). Likewise, interventions targeting mitochondrial function, autophagy, or protein quality control must account for their essential roles in maintaining cellular homeostasis (Pickles et al., 2018).

These considerations motivate a potential strategy that we term *precision memory editing*: identifying the molecular mechanisms responsible for maintaining a pathological cellular state and selectively targeting the relevant regulatory nodes, while leaving unrelated protective responses intact. Implementing this approach would require biomarkers that distinguish cells carrying persistent, maladaptive changes from those undergoing a normal, reversible stress response. It would also require evidence that the targeted changes persist after the original stress has been removed and contribute directly to the pathological phenotype. Although precision memory editing remains a proposed framework rather than an established therapeutic modality, it offers a way to organize future research around the mechanisms that maintain cellular stress memory rather than pathway activation alone.

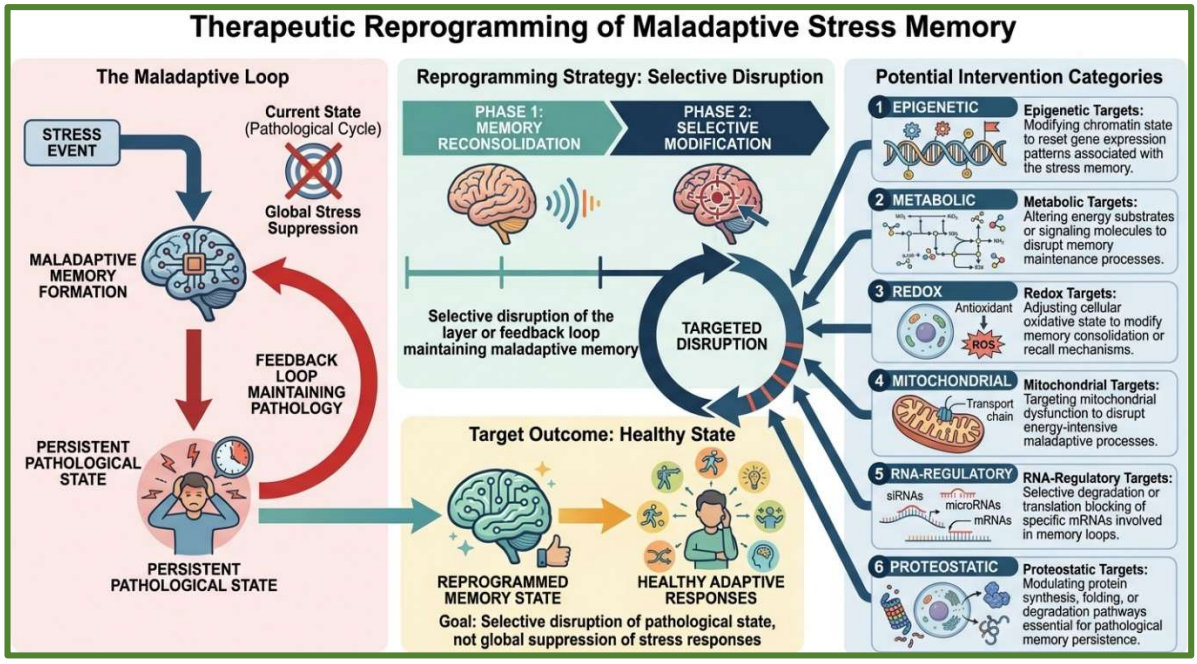


Figure 4. **Paradigm for therapeutic reprogramming of stress memory. Selective disruption of pathological memory loops. Persistent maladaptive memory maintains disease states through self-reinforcing feedback. Precision memory editing employs a two-phase strategy (reconsolidation followed by targeted modification) across six molecular nodes epigenetic, metabolic, redox, mitochondrial, RNA, and proteostatic to restore healthy cell function without global stress suppression.**

7. Disease Contexts and the Unifying Logic

The multilayer framework can integrate observations from several disease contexts without claiming that all are mechanistically identical. Metabolic memory in diabetes demonstrates persistence after normalization of the initiating metabolic disturbance. Trained immunity demonstrates durable functional reprogramming of innate immune cells after an earlier stimulus. Cancer therapy resistance can involve stable transcriptional, chromatin, metabolic, and proteostatic states that alter drug responsiveness. Ageing is associated with accumulated mitochondrial, epigenetic, proteostatic, and inflammatory changes that can modify responses to new stressors.

These contexts share a general logic but should not be collapsed into one phenomenon. Trained immunity is a specialized immunological state; metabolic memory emphasizes persistent consequences of metabolic exposure; and therapeutic resistance includes genetic, epigenetic, phenotypic, and microenvironmental mechanisms. The value of this framework is therefore not to rename these fields, but to identify shared principles and testable connections among them.

8. Future Perspectives

A major challenge in understanding cellular stress memory is determining when a transient response becomes a persistent state and why this transition produces beneficial adaptation in some circumstances but pathological changes in others. Future studies should establish the minimum intensity and duration of stress required to induce persistent changes across different cell types and biological contexts. Equally important is identifying which molecular layer responds first and which mechanisms ultimately maintain the altered state after the original stress has subsided. Addressing these questions will help distinguish the initial encoding of stress from the processes responsible for its long-term persistence.

Another priority is to determine whether the pre-existing cellular state influences the likelihood of developing adaptive or maladaptive memory. Age, metabolic status, mitochondrial function, epigenetic background, and previous stress exposure may shape this response. Integrating these factors with single-cell transcriptomics, epigenomic profiling, and other multi-omics approaches could help identify subpopulations that retain persistent stress-associated changes. However, molecular signatures alone will not establish memory; longitudinal studies and functional experiments will be needed to determine whether these changes persist and alter responses to subsequent challenges.

A further objective is to establish whether maladaptive stress memory can be selectively reversed without compromising beneficial adaptation. This will require identifying the regulatory mechanisms that maintain pathological states and testing whether their targeted disruption restores normal cellular function. Such work could also clarify whether manipulating the balance between adaptive and maladaptive responses improves resilience or, conversely, increases susceptibility to disease. The challenge will be to intervene at the mechanisms sustaining pathological persistence rather than broadly suppressing stress-response pathways that remain essential for cellular homeostasis.

Translating these findings into clinical practice will require biomarkers capable of detecting persistent stress-associated states and distinguishing them from normal, reversible responses. Researchers should investigate whether such signatures predict treatment response, disease relapse, or treatment-related toxicity. Longitudinal patient studies, combined with causal multi-omics approaches and experimental validation, will be essential to determine whether these signatures reflect mechanisms of persistence or merely correlate with disease severity.

Ultimately, progress in this field will depend on moving beyond the identification of stress-responsive pathways toward a mechanistic understanding of how cellular states are established, maintained, and potentially reversed. This framework may provide a foundation for future strategies designed to selectively modify maladaptive cellular memory while preserving protective adaptation. Achieving this goal will require careful validation across biological models and clinical settings before stress-memory-directed interventions can be considered therapeutically actionable.

9. Conclusion

Cellular stress responses are often described as transient adaptations, but increasing evidence indicates that some stress-induced states persist and alter future cellular behavior. The proposed multilayer stress-memory framework emphasizes that persistence is unlikely to reside in a single molecule or pathway. Instead, it may emerge from reciprocal interactions among epigenetic, transcriptional, metabolic, mitochondrial, RNA-regulatory, proteostatic, and inflammatory networks. The most important experimental distinction is between a stress response that remains active and a genuine memory state that persists after stress withdrawal and changes the response to a subsequent challenge. Establishing this distinction will be essential for translating cellular memory into mechanistic biology and therapeutic strategy. The central future challenge is selective reprogramming: removing maladaptive molecular memory while preserving the adaptive information that allows cells to survive future stress.

Declaration of Generative AI and AI-Assisted Technologies

Google Gemini was used to generate the figures and conceptual illustrations presented in this review article. Generative AI tools were also used to assist in polishing the manuscript's language and improving its clarity and readability. The author reviewed and critically evaluated the generated figures and all AI-assisted textual edits and takes full responsibility for the accuracy, integrity, and final content of the manuscript.

Data Availability Statement

No new datasets were generated or analyzed during this review. All information discussed in the article is derived from previously published literature, which is cited in the manuscript.

Author Contributions

The author was responsible for conceptualization, literature review, synthesis and interpretation of the available evidence, manuscript preparation, critical revision, and final approval of the manuscript.

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