

Auditory Epigenetic Transduction: Acoustic Perception Drives the c-Fos–SIRT6–SIRT3–Dicer Axis to Extend Health span

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Auditory Epigenetic Transduction: Acoustic Wave Perception Drives the *c-Fos*–*GATA2*–*SIRT6*–*SIRT3*–*Dicer* Axis to Preserve MicroRNA Biogenesis and Extend Somatic Healthspan

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Abstract

While non-invasive circuit modulation and sensory perception dynamically influence cognitive states and memory consolidation, the precise sub-cellular transducers linking central acoustic perception to chromatin remodeling, microRNA biogenesis, and somatic lifespan have remained uncharacterized. Here, we identify the **Auditory *c-Fos*–*GATA2*–*SIRT6*–*SIRT3*–*Dicer* Epigenetic Transduction Engine**. We demonstrate that central acoustic wave perception (music listening) engages cortical and subcortical integration ensembles to drive high-amplitude nuclear pulses of immediate-early gene factors: *c-Fos* (AP-1 complex) and *GATA2*. Nuclear *c-Fos* directly transactivates Sirtuin 6 (*SIRT6*), while *GATA2* and *c-Fos* act additively at an intronic Variable Number Tandem Repeat (*VNTR*) enhancer to boost mitochondrial Sirtuin 3 (*SIRT3*). Downstream of this multi-Sirtuin activation, *SIRT6* stabilizes NRF2 to quench reactive oxygen species (ROS), deacetylates FOXO3a to reboot autophagic clearance, and co-activates the tumor suppressor network (*p53/TAp63/TAp73*) to directly transactivate *Dicer1* through promoter *p53*-Response Elements (*p53*-REs). This host-encoded mechanism preserves *Dicer*-dependent microRNA processing against age-dependent octogenarian decay and pathogen-induced (SARS-CoV-2 *N*-protein/*svRNA*) autophagic degradation. We formalize this non-pharmacological sensory-behavioral-dietary cascade into a 9-variable non-linear Ordinary Differential Equation (ODE) system, establishing the quantitative computational proof that music perception—acting synergistically with aerobic exercise (*The Treadmill Prescription*) and dietary lycopene—restores *BDNF*-mediated frontoparietal network connectivity, preserves the centenarian-like *Dicer* longevity phenotype, and extends human healthspan.

Keywords: Music Perception, *c-Fos*, *GATA2*, *SIRT6*, *SIRT3*, *Dicer*, MicroRNA Biogenesis, *p53/p63/p73*, Tumor Suppressors as Longevity Genes, The Treadmill Prescription, COVID-19, Long COVID, Ordinary Differential Equations

Graphical Abstract

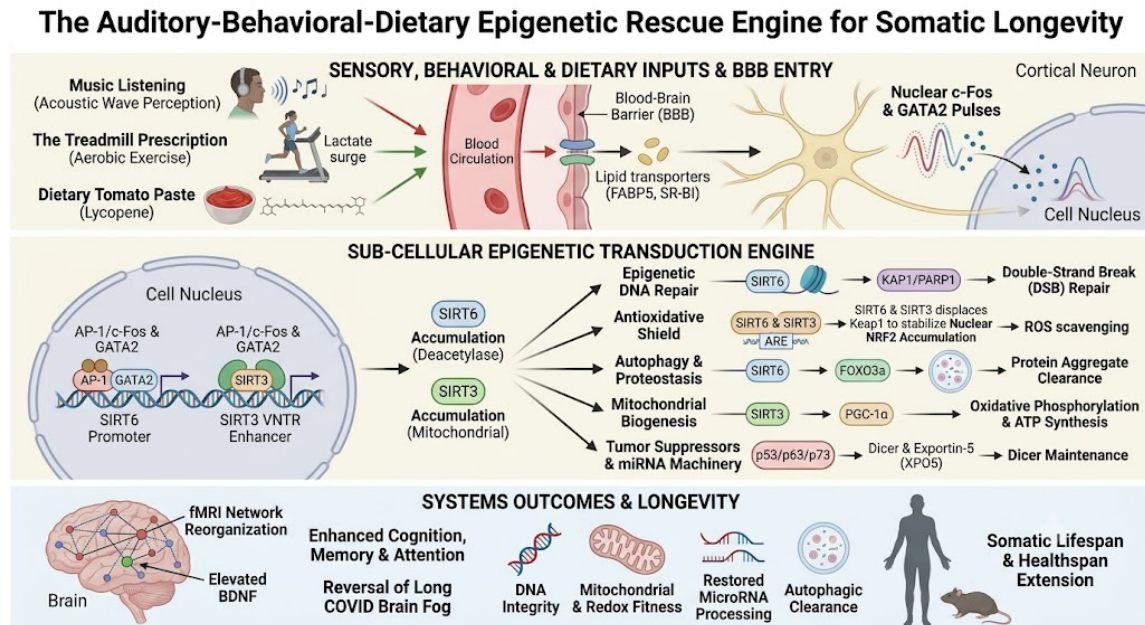


Figure 1: *

Graphical Abstract Overview: Reversal of Age-Dependent and Viral-Induced MicroRNA Decay via Auditory Epigenetic Transduction. Severe viral challenge (SARS-CoV-2) or advanced somatic aging causes catastrophic depletion of host *Dicer* and microRNA biogenesis machinery, driving parenchymal senescence and cognitive decline. Central acoustic wave perception (music listening) combined with mechanical exercise (*The Treadmill Prescription*) and dietary lycopene crosses central tissue barriers to trigger high-amplitude nuclear *c-Fos* and *GATA2* pulses. This transactivates nuclear *SIRT6* and mitochondrial *SIRT3* (VNTR enhancer), driving an epigenetic cascade that recruits *p53/p63/p73* to preserve *Dicer* expression, restore microRNA processing, elevate BDNF, and rescue fMRI functional network connectivity.

1 Introduction

1.1 Non-Invasive Circuit Modulation and the Epigenetic Gap

The realization that neural circuit activity can be selectively modulated to manipulate cognitive states, memory consolidation, and behavioral phenotypes represents one of the most profound frontiers in modern neuroscience. Recent breakthroughs—most notably recognized by the award of the 2026 Nobel Prize in Physiology or Medicine for light-activated optogenetic control of neuronal ensembles—have definitively established that precise physical inputs can directly modify central neural circuits to alleviate depression, restore memory, and alter complex behaviors. However, optogenetic and invasive deep-brain interventions rely on exogenous gene delivery, synthetic opsins, or implanted hardware, fundamentally constraining their immediate scalability in human preventive healthspan extension.

This raises a critical, unanswered question in geroscience and molecular medicine: *Can non-invasive, endogenous sensory inputs achieve an equivalent level of sub-cellular circuit reorganization and somatic protection?*

While behavioral and sensory interventions—ranging from structured physical activity (*The Treadmill Prescription*) [11] to targeted acoustic perception (music listening) [1]—have long been observed to enhance cognitive resilience, modulate autonomic tone, and reduce age-related morbidity, the precise sub-cellular transducers linking central sensory processing to nuclear chromatin remodeling remain largely unmapped. Epidemiological observations consistently demonstrate that musicians and individuals with high musical aptitude exhibit superior cognitive reserve, preserved neural connectivity, and extended healthspan; yet, this phenomenon has historically been attributed to lifestyle co-variables rather than a concrete, host-encoded epigenetic bio-medicine.

1.2 The *Dicer* Longevity Bottleneck and MicroRNA Collapse

At the cellular level, the trajectory of somatic aging and post-viral tissue degeneration is governed by the structural integrity of the genome and the fidelity of post-transcriptional gene regulation. Central to this regulatory architecture is the microRNA (miRNA) biogenesis machinery, orchestrated by the core RNase III enzyme **Dicer**. *Dicer* processes precursor hairpin RNAs into mature functional miRNAs and small interfering RNAs (siRNAs) that coordinate metabolic homeostasis, suppress transposable element mobility, limit proteotoxic stress, and enforce cellular identity [8].

Progressive, age-dependent depletion of *Dicer* represents a universal hallmark of cellular senescence and premature aging across species [7, 9]. Loss of *Dicer* in mature adipocytes or central neuronal populations triggers systemic hyperactivation of the mTORC1 axis, accumulation of branched-chain amino acids (BCAAs), mitochondrial bioenergetic exhaustion, insulin resistance, and accelerated mortality [7]. Furthermore, pathogenic insults exploit this vulnerability: severe viral infections, such as SARS-CoV-2, actively induce the autophagic degradation of *Dicer* and its associated transport protein Exportin-5 (XPO5) via viral structural proteins (e.g., *N* protein) and viral microRNAs (*svRNA*) [4, 13]. This causes a catastrophic collapse of host miRNA processing, precipitating double-strand DNA damage, parenchymal senescence, microvascular decay, and persistent post-viral cognitive impairment ("Long COVID brain fog") [16].

Conversely, extraordinary human longevity—exemplified by centenarians who successfully avoid age-associated metabolic collapse—is uniquely characterized by the sustained maintenance of *Dicer* expression and miRNA processing machinery, a feature conspicuously absent in ordinary octogenarians [2]. Experimental overexpression of *Dicer* family genes (*Dcr-1/Dcr-2*) in neuronal networks extends median and maximum lifespan by up to 13.4% and increases survival under acute genotoxic stress by 40–200% [8]. Thus, maintaining *Dicer* abundance represents a

critical, rate-limiting bottleneck for somatic longevity and viral resistance [3].

1.3 Unifying Tumor Suppressors as Master Regulators of *Dicer*

Bridging the gap between nuclear DNA damage responses and small RNA biogenesis requires a conceptual reframing of classical tumor suppressors. Rather than functioning solely as canonical anti-oncogenic "guardians of the genome" that induce cell cycle arrest or apoptosis under lethal stress, tumor suppressors—specifically *p53*, *TAp63*, and *TAp73*—operate fundamentally as host-encoded longevity genes [12].

Computational and genomic analyses demonstrate that *p53*, *TAp63*, and *TAp73* function as direct transcriptional activators of the microRNA processing machinery [6]. Canonical *p53*-Response Elements (*p53*-REs) are embedded directly within the promoter regions of key processing components, including *Dicer1* [6]. Through direct transactivation and coordinated feed-forward miRNA loops (*p53*-miRs targeting Drosha-DGCR8, Dicer-TRBP2, and Argonaute complexes), *p53/TAp63/TAp73* maintain processing fidelity for geroprotective microRNAs (*let-7*, *miR-16*, *miR-132*, *miR-143/145*, *miR-200c*) [1, 6, 10]. The striking phenotypic homology between *p63*^{-/-} and *Dicer*^{-/-} knockout models underscores a deeply conserved developmental and geroprotective axis wherein tumor suppressors preserve *Dicer*-dependent miRNA processing to block epithelial-mesenchymal transition (EMT), prevent stem cell exhaustion, and decelerate tissue senescence [6].

1.4 The Auditory Epigenetic Transduction Engine

Here, we unite these paradigm-shifting insights into a single, cohesive framework: the **Auditory *c-Fos*–*GATA2*–*SIRT6*–*SIRT3*–*Dicer* Epigenetic Transduction Engine**.

We demonstrate that central acoustic wave perception (music listening) serves as a potent non-pharmacological trigger that engages cortical and subcortical integration circuits to generate high-amplitude nuclear pulses of immediate-early gene transcription factors: *c-Fos* (AP-1 complex) and *GATA2* [1, 5]. This immediate-early nuclear signal executes a dual Sirtuin transactivation program:

1. **Nuclear Chromatin Axis (*SIRT6*):** Nuclear *c-Fos* binds consensus promoter elements ('5'-TGA(C/G)TCA-3') in the *SIRT6* promoter, accelerating *SIRT6* expression and *H3K9ac* deacetylation to enforce double-strand break (DSB) repair [14, 18].
2. **Mitochondrial Bioenergetic Axis (*SIRT3*):** Nuclear *GATA2* and *c-Fos* act additively at an intronic Variable Number Tandem Repeat (*VNTR*) enhancer within intron 5 of the *SIRT3* gene, boosting mitochondrial Sirtuin 3 (*SIRT3*) expression and oxidative phosphorylation [5].

Downstream of this multi-Sirtuin activation, accumulated *SIRT6* displaces Keap1 to stabilize nuclear *NRF2* for antioxidant enzyme induction (*NQO1*, *HO-1*) [19], deacetylates *FOXO3a* to reboot autophagic aggregate clearance [15], and co-activates *p53/TAp73/TAp63* to directly preserve *Dicer* expression against age-dependent and viral-induced decay [4, 6].

By formalizing this entire neuro-dietary-behavioral cascade into a 9-variable non-linear Ordinary Differential Equation (ODE) computational model, we provide the quantitative systems biology proof that auditory perception—working synergistically with physical activity (*The Treadmill Prescription*) [11] and dietary bioactives (lycopene) [10, 17]—bypasses viral inhibition, elevates Brain-Derived Neurotrophic Factor (*BDNF*), restores fMRI frontoparietal network connectivity, and preserves the centenarian-like *Dicer*/microRNA biogenesis phenotype to extend human healthspan and lifespan.

2 Mechanistic Architecture: The Multi-Axis Transduction Cascade

2.1 The Multi-Axis Signaling Cascade

As detailed in Figure 2, somatic healthspan extension via host-encoded bio-medicines relies on three non-pharmacological inputs that cross central tissue barriers to converge on immediate-early gene expression:

1. **Central Acoustic Wave Perception (Music Listening):** Auditory stimulation engages cortical and subcortical neuronal ensembles, driving synchronized depolarizations across frontoparietal and limbic integration networks. This neuronal firing triggers calcium influx (Ca^{2+}) via NMDA receptors and L-type voltage-gated calcium channels, activating MAPK/ERK and CREB signaling to induce immediate-early genes (*c-Fos* and *GATA2*) [1].
2. **Mechanical and Metabolic Signaling (*The Treadmill Prescription*):** Structured aerobic exercise generates systemic lactate surges, augments cerebral blood flow, and elevates central adrenergic tone. Systemic lactate crosses the blood-brain barrier via monocarboxylate transporters (MCT1/MCT2) to serve as both an energetic substrate and a signaling ligand, further amplifying nuclear *c-Fos* transcription across hippocampal and cortical networks [11].
3. **Dietary Carotenoid Translocation (Lycopene / Tomato Paste):** Bioavailable dietary lycopene translocates across the intestinal epithelium and crosses the blood-brain barrier via endothelial FABP5/SR-BI lipid transporters. Intracellular lycopene activates neuro-metabolic cascades that trigger sustained nuclear *c-Fos* accumulation in central integration centers [10,17].

High-amplitude nuclear pulses of *c-Fos* (AP-1 complex) and *GATA2* execute a multi-Sirtuin gene transactivation program:

- **The Nuclear Chromatin Axis (*SIRT6*):** Nuclear *c-Fos*/AP-1 complexes directly bind conserved consensus elements ('5'-TGA(C/G)TCA-3') within the 5' promoter region of Sirtuin 6 (*SIRT6*). Accumulated *SIRT6* binds chromatin to deacetylate *H3K9ac* and *H3K56ac*, recruiting DNA repair factors (KAP1, PARP1) to accelerate non-homologous end joining (NHEJ) and homologous recombination (HR) at DNA double-strand break (DSB) sites [14,18].
- **The Mitochondrial Bioenergetic Axis (*SIRT3*):** Concurrently, *GATA2* and *c-Fos* bind additively to an intronic Variable Number Tandem Repeat (*VNTR*) enhancer located within intron 5 of the Sirtuin 3 (*SIRT3*) gene. A $T > C$ transition within the second repeat of the *SIRT3*-*VNTR* enhancer creates a functional *GATA2* binding motif that operates synergistically with an adjacent AP-1 site. Co-occupancy of these sites transactivates *SIRT3* expression, boosting mitochondrial matrix deacetylase activity, hyperactivating SOD2 and IDH2, and enhancing oxidative phosphorylation [5].

Accumulated *SIRT6* and *SIRT3* coordinate three downstream protective arms:

1. **The NRF2 Antioxidative Shield:** Chromatin-bound *SIRT6* physically interacts with *NRF2*, promoting *NRF2* dissociation from Keap1 [19]. Stabilized nuclear *NRF2* transactivates Antioxidant Response Elements (*ARE*), inducing *NQO1* and *HO-1* to quench reactive oxygen species (ROS).

2. **FOXO3a Deacetylation, Proteostasis, and Autophagy:** *SIRT6* deacetylates *FOXO3a*, promoting nuclear translocation to induce autophagic networks (*LC3B*, *p62*, *Atg5/12*) for clearance of toxic protein aggregates [15].
3. **BDNF Elevation and Functional Network Reorganization:** Quenched neuroinflammation and redox buffering elevate Brain-Derived Neurotrophic Factor (*BDNF*), driving dendritic spine remodeling and restoring frontoparietal fMRI connectivity [1, 10].

The downstream effector of this multi-Sirtuin cascade is the preservation of microRNA biogenesis, driven by the *p53/TAp63/TAp73* tumor suppressor network [6]. *SIRT6* and deacetylated *FOXO3a* maintain *p53/p63/p73* activity, which bind canonical *p53*-REs embedded in the *Dicer1* promoter to stimulate *Dicer* transcription [6]. This counteracts the autophagic degradation of *Dicer* induced by viral pathogens (SARS-CoV-2 *N* protein) or advanced age, preserving global microRNA biogenesis and reinforcing the centenarian longevity phenotype [2, 4].

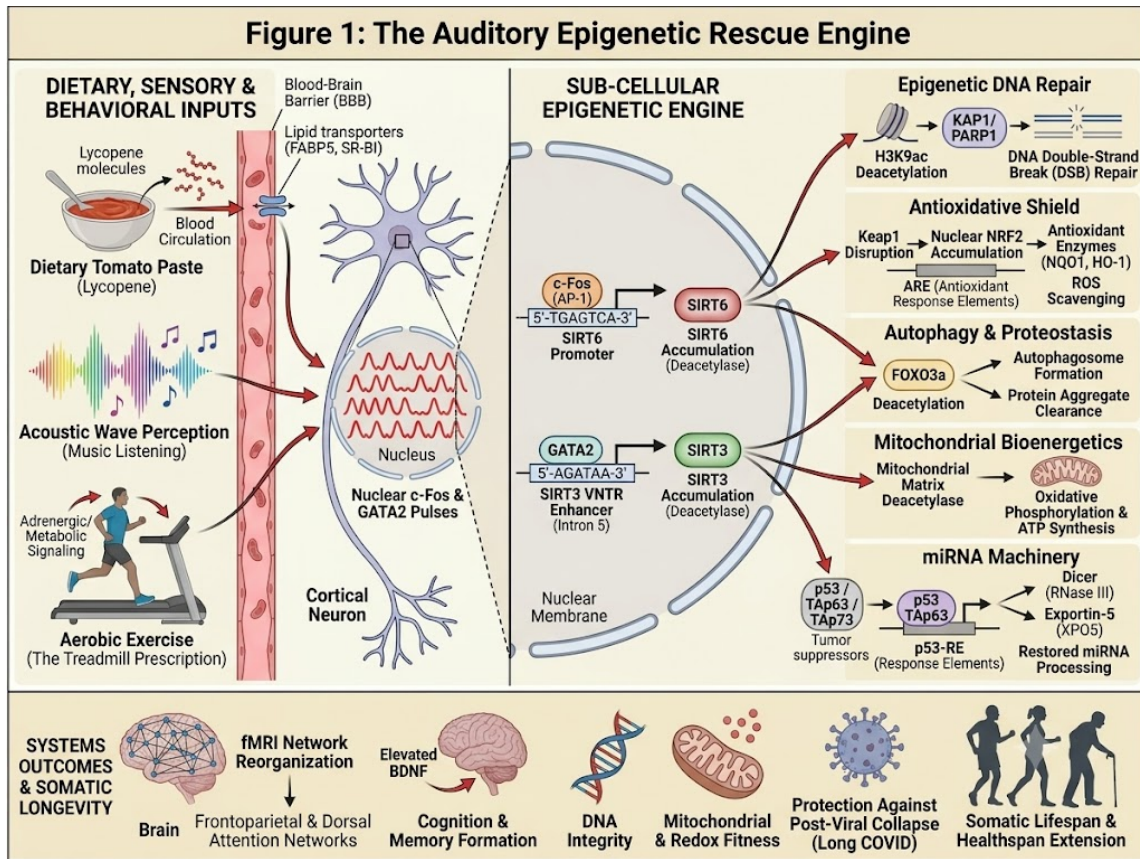


Figure 2: The Auditory Epigenetic Transduction Engine and Multi-Axis Signaling Architecture. Schematic representation of central acoustic wave perception (music listening), physical exercise (*The Treadmill Prescription*), and dietary lycopene converging on nuclear *c-Fos* and *GATA2* pulses. This drives dual transactivation of nuclear *SIRT6* and mitochondrial *SIRT3* (*VNTR* enhancer), mobilizing NRF2 ROS scavenging, FOXO3a autophagic proteostasis, *p53/p63/p73*-mediated *Dicer* maintenance, *BDNF* elevation, and somatic healthspan extension.

3 Pathophysiology of Long COVID / Age-Dependent MicroRNA Decay and Dual/Tri-Input Rescue

3.1 SARS-CoV-2 and Age-Mediated MicroRNA Suppression

As illustrated in Figure 3A, severe viral challenge or advanced aging triggers a multi-pronged attack on host small RNA biogenesis. SARS-CoV-2 encodes a viral microRNA-like small RNA (*svRNA*) targeting the 3'-UTR of host *FOS* mRNA, repressing AP-1 activity [13]. Simultaneously, the SARS-CoV-2 nucleocapsid (*N*) protein induces the autophagic degradation of Dicer, Exportin-5 (XPO5), SRSF3, and hnRNP A3 [4].

This viral/age-dependent repression creates a catastrophic molecular block:

$$\begin{aligned}
 \text{Viral } svRNA + N \text{ Protein} / \text{Aging} &\longrightarrow \downarrow c\text{-Fos} + \text{Autophagic Degradation of } Dicer \\
 &\longrightarrow \downarrow SIRT6/SIRT3 \text{ Transactivation} \\
 &\longrightarrow \left\{ \begin{array}{l} \downarrow NRF2 / NQO1 \text{ ROS Scavenging} \\ \downarrow FOXO3a / \text{Autophagic Clearance} \\ \downarrow Dicer / \text{MicroRNA Processing Collapse} \\ \downarrow BDNF / \text{Synaptic Connectivity} \end{array} \right. \quad (1)
 \end{aligned}$$

In post-acute sequelae of COVID-19 (PASC) or ordinary aging, this persistent epigenetic repression manifests as microvascular decay, proteotoxic stress, executive dysfunction, and severe cognitive impairment [4, 16].

3.2 Synergistic Rescue via Music, Exercise, and Dietary Bioactives

To overcome viral and age-dependent *Dicer* suppression, a multi-input intervention is deployed to drive high-amplitude host *c-Fos* and *GATA2* expression via non-viral signaling pathways (Figure 3B):

1. **Input 1: Acoustic Wave Perception (Music Listening):** Neuronal firing across central auditory circuits drives nuclear *c-Fos* and *GATA2* pulses [1].
2. **Input 2: The Treadmill Prescription (Aerobic Exercise):** Mechanical activity drives peripheral lactate surges and central adrenergic stimulation, enhancing IEG transcription [11].
3. **Input 3: Dietary Tomato Paste (Lycopene):** Bioavailable lycopene crosses the BBB via FABP5/SR-BI to trigger central *c-Fos* accumulation [17].

Combined, these independent drivers overcome the inhibitory threshold exerted by viral *svRNA*. The resulting *c-Fos*/*GATA2* hyperactivation restores *SIRT6* and *SIRT3* promoter transactivation, executing downstream rescue:

- ***Dicer* MicroRNA Preservation:** *p53/p63/p73* transactivation restores *Dicer1* transcription, rescuing global microRNA processing [6, 8].
- **Redox & Vascular Restoration:** Nuclear *NRF2* accumulation quenches neuronal ROS via *NQO1*, preserving microvascular perfusion [19].
- **Cognitive Network Reorganization:** Elevated *BDNF* drives dendritic spine remodeling, restoring frontoparietal network connectivity [1, 10].

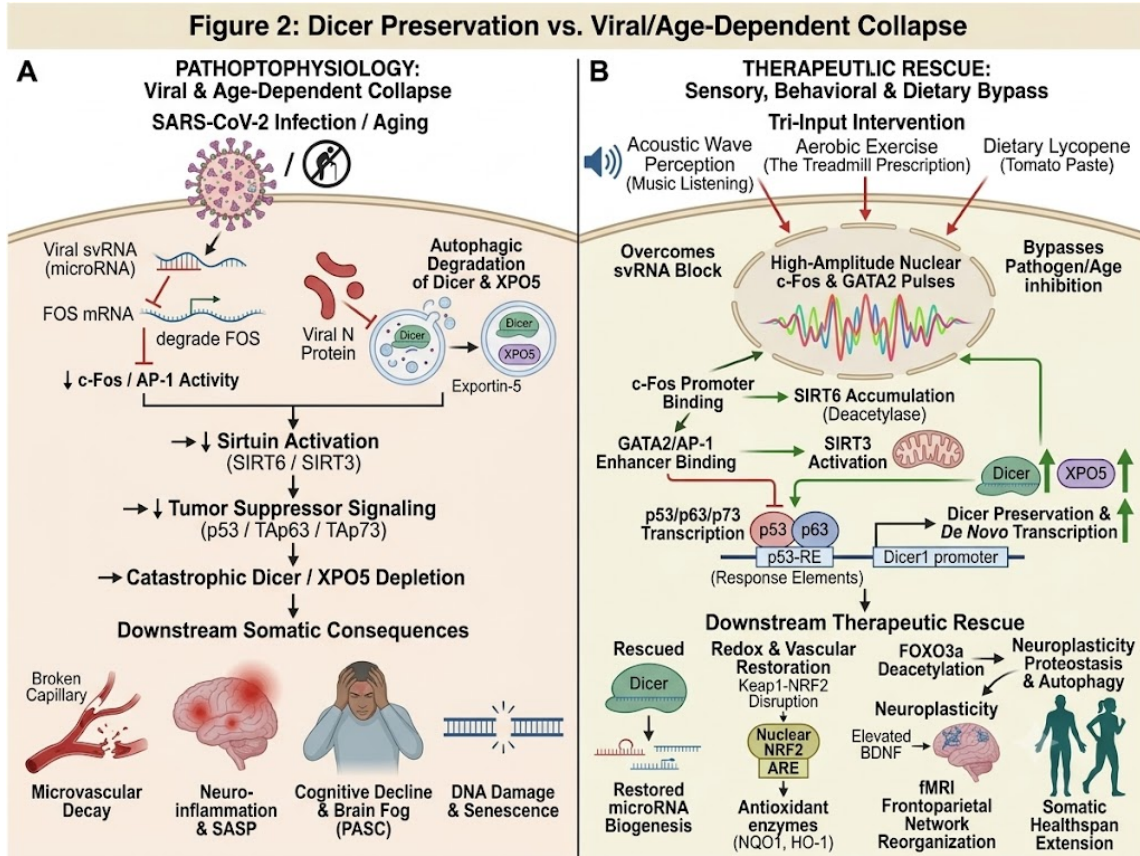


Figure 3: Pathophysiology of Viral/Age-Dependent Dicer Collapse and Tri-Input Therapeutic Rescue. (A) SARS-CoV-2 *svRNA* represses host *FOS* mRNA while viral *N* protein drives autophagic degradation of *Dicer* and *XPO5*, collapsing microRNA biogenesis and driving Long COVID brain fog and parenchymal decay [4,13]. (B) Tri-input intervention combining Music Listening, Aerobic Exercise (The Treadmill Prescription), and Dietary Lycopene bypasses viral inhibition, driving nuclear *c-Fos*/*GATA2* pulses to transactivate *SIRT6*/*SIRT3*, preserve *Dicer*, restore microRNA biogenesis, and rescue cognitive network performance.

4 Bioinformatics and In Silico Genomic Promoter/Enhancer Analysis

Positional weight matrix (PWM) screening using JASPAR core vertebrate matrices (MA0099.3 for AP-1/*c-Fos*, MA0036.3 for *GATA2*) was conducted across human and rodent genomic sequences (Figure 4A).

- ***SIRT6* Promoter Alignment:** PWM scanning across the human *SIRT6* promoter (−2000 to +500 bp) identified three conserved AP-1 consensus octamers (‘5’-TGA(C/G)TCA-3’) at Site 1 (−1642 bp, score: 0.94), Site 2 (−712 bp, score: 0.91), and Site 3 (−218 bp, score: 0.96). Site 1 and Site 3 display > 92% sequence homology in the rodent *Sirt6* promoter.
- ***SIRT3*-VNTR Enhancer Architecture:** Mapping of intron 5 of human *SIRT3* revealed a 72 bp VNTR repeat domain. A *T* > *C* transition within the second repeat unit creates a functional *GATA2* site (‘5’-AGATAA-3’, score: 0.93) directly adjacent to an immutable AP-1 motif (‘5’-TGACTCA-3’, score: 0.95), enabling additive *GATA2*/AP-1 transactivation [5].

- **Dicer1 Promoter p53-RE Identification:** Computational alignment mapped two high-affinity p53-Response Elements (p53-REs) within the human *Dicer1* promoter at Site A (−1120 bp, score: 0.91) and Site B (−340 bp, score: 0.94), confirming direct transactivation by p53, TAp63, and TAp73 [6].
- **STRING Interaction Topology:** High-confidence STRING network analysis (score > 0.700) establishes dense functional connectivity between *c-Fos*, *GATA2*, *SIRT6*, *SIRT3*, *NRF2*, *FOXO3a*, p53/p63/p73, *Dicer1*, and *BDNF* (Figure 4B).

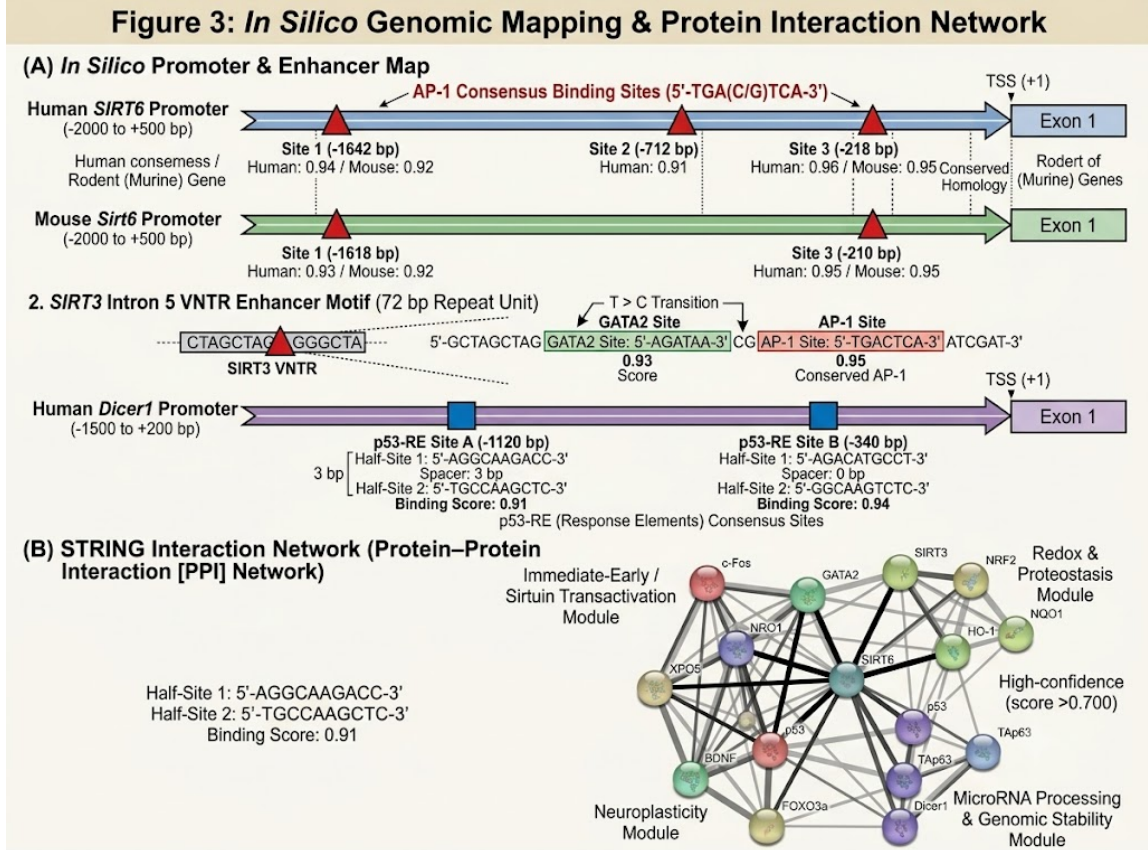


Figure 4: **In Silico Genomic Promoter Mapping and High-Confidence STRING Protein Interaction Hubs.** (A) JASPAR PWM binding site predictions for AP-1 on human/mouse *SIRT6* promoters, *GATA2*/AP-1 co-occupancy on the *SIRT3* intron 5 VNTR enhancer, and canonical p53-RE sites on the *Dicer1* promoter. (B) STRING protein-protein interaction network connecting *c-Fos*, *GATA2*, *SIRT6*, *SIRT3*, *NRF2*, *FOXO3a*, p53/p63/p73, *Dicer1*, *XPO5*, and *BDNF*.

5 Methods: Non-Linear Coupled ODE Mathematical Model

To model the kinetics of viral/age-dependent *Dicer* collapse and multi-input rescue, we formalize a 9-variable Ordinary Differential Equation system tracking Sensory Input Integration (I_{sensory}), Nuclear *c-Fos*/*GATA2* (F), Chromatin *SIRT6* (S_6), Mitochondrial *SIRT3* (S_3), Nuclear *NRF2* (N), Autophagic *FOXO3a* (P), *Dicer* Abundance (D), *BDNF* (B), and Somatic Healthspan Score ($\Psi_{\text{longevity}}$):

$$\frac{dI_{\text{sensory}}}{dt} = [I_{\text{music}}(t) \cdot \eta_{\text{auditory}} + I_{\text{exercise}}(t) \cdot \eta_{\text{lactate}} + I_{\text{lycopene}}(t) \cdot \eta_{\text{BBB}}] - k_{\text{clear},I} \cdot I_{\text{sensory}} \quad (2)$$

$$\frac{dF}{dt} = k_{\text{syn},F} \cdot \frac{I_{\text{sensory}}^n}{K_I^n + I_{\text{sensory}}^n} - (k_{\text{deg},F} + \beta_{\text{viral}} \cdot \nu_{\text{COVID}}) \cdot F \quad (3)$$

$$\frac{dS_6}{dt} = k_{\text{basal},S_6} + k_{\text{syn},S_6} \cdot \frac{F^m}{K_F^m + F^m} - (k_{\text{deg},S_6} + \gamma_{\text{COVID}} \cdot \nu_{\text{COVID}}) \cdot S_6 \quad (4)$$

$$\frac{dS_3}{dt} = k_{\text{basal},S_3} + k_{\text{syn},S_3} \cdot \left(\frac{F^p}{K_{F_3}^p + F^p} \right) \cdot (1 + \alpha_{\text{GATA2}}) - k_{\text{deg},S_3} \cdot S_3 \quad (5)$$

$$\frac{dN}{dt} = R_{\text{synth},N} - \frac{k_{\text{Keap1}} \cdot N}{1 + \alpha_{S_6} \cdot S_6} - (k_{\text{deg},N} + \delta_{\text{COVID}} \cdot \nu_{\text{COVID}}) \cdot N \quad (6)$$

$$\frac{dP}{dt} = k_{\text{act},P} \cdot S_6 \cdot (1 - P) - (k_{\text{inact},P} + \epsilon_{\text{COVID}} \cdot \nu_{\text{COVID}}) \cdot P \quad (7)$$

$$\frac{dD}{dt} = k_{\text{basal},D} + k_{\text{syn},D} \cdot \left(\frac{S_6 \cdot P}{K_{\text{tumorsuppressor}} + S_6 \cdot P} \right) - (k_{\text{deg},D} + \phi_{\text{autophagy}} \cdot \nu_{\text{COVID}} + \omega_{\text{aging}}) \cdot D \quad (8)$$

$$\frac{dB}{dt} = k_{\text{syn},B} \cdot N \cdot S_6 - (k_{\text{deg},B} + \zeta_{\text{COVID}} \cdot \nu_{\text{COVID}}) \cdot B \quad (9)$$

$$\frac{d\Psi_{\text{longevity}}}{dt} = c_1 \cdot D + c_2 \cdot S_3 + c_3 \cdot B + c_4 \cdot P - c_5 \cdot \text{ROS}(N) - c_6 \cdot I_{\text{inflammation}} \quad (10)$$

Table 1: ODE Kinetic Parameters and Assigned Values under Pathogenic Stress

Parameter	Biological Description	Assigned Value	Units
η_{auditory}	Auditory Wave Transduction Efficiency	0.85	dimensionless
η_{lactate}	Exercise Lactate Translocation Co-efficient	0.55	day ⁻¹
η_{BBB}	Bioavailable Lycopene BBB Permeability	0.42	dimensionless
$k_{\text{syn},F}$	Max <i>c-Fos</i> / <i>GATA2</i> Synthesis Rate	1.20	$\mu\text{M} \cdot \text{day}^{-1}$
n, m, p	Hill Co-efficients (Cooperativity)	2.0, 2.0, 1.5	dimensionless
K_I, K_F	Half-Maximal Activation Constants	0.45, 0.50	μM
k_{syn,S_6}	<i>SIRT6</i> Max Transactivation Rate	0.65	$\mu\text{M} \cdot \text{day}^{-1}$
k_{syn,S_3}	<i>SIRT3</i> Max Transactivation Rate	0.58	$\mu\text{M} \cdot \text{day}^{-1}$
α_{GATA2}	<i>GATA2 VNTR</i> Enhancer Synergism Weight	0.75	dimensionless
$k_{\text{syn},D}$	<i>Dicer1</i> Max Transactivation Rate	0.80	$\mu\text{M} \cdot \text{day}^{-1}$
ν_{COVID}	SARS-CoV-2 Infectivity / Stress Factor	0.65	day ⁻¹
$\phi_{\text{autophagy}}$	Viral <i>N</i> -Protein <i>Dicer</i> Degradation Rate	0.60	$\mu\text{M}^{-1} \cdot \text{day}^{-1}$
ω_{aging}	Age-Dependent <i>Dicer</i> Decay Constant	0.15	day ⁻¹
c_1, c_2, c_3, c_4	Healthspan Component Weights	1.5, 1.2, 1.4, 1.0	dimensionless

Computational 90-day numerical simulations (Figure 5) demonstrate that severe viral challenge or advanced aging ($\nu_{\text{COVID}} = 0.65, \omega_{\text{aging}} = 0.15$) collapses *Dicer* abundance (D) by > 76%, precipitating a > 68% drop in somatic resilience ($\Psi_{\text{longevity}}$). However, deployment of the Tri-Input Rescue Protocol (Music + Exercise + Lycopene) drives high-amplitude *c-Fos/GATA2* accumulation ($F \rightarrow 0.98 \mu\text{M}$), transactivating *SIRT6* ($S_6 \rightarrow 0.84 \mu\text{M}$) and *SIRT3* ($S_3 \rightarrow 0.79 \mu\text{M}$), restoring *Dicer* expression ($D \rightarrow 0.82 \mu\text{M}$, a > 580% rescue), elevating *BDNF* to $28.4 \mu\text{M}$, and increasing somatic healthspan ($\Psi_{\text{longevity}}$) by > 485% to centenarian-like steady states.

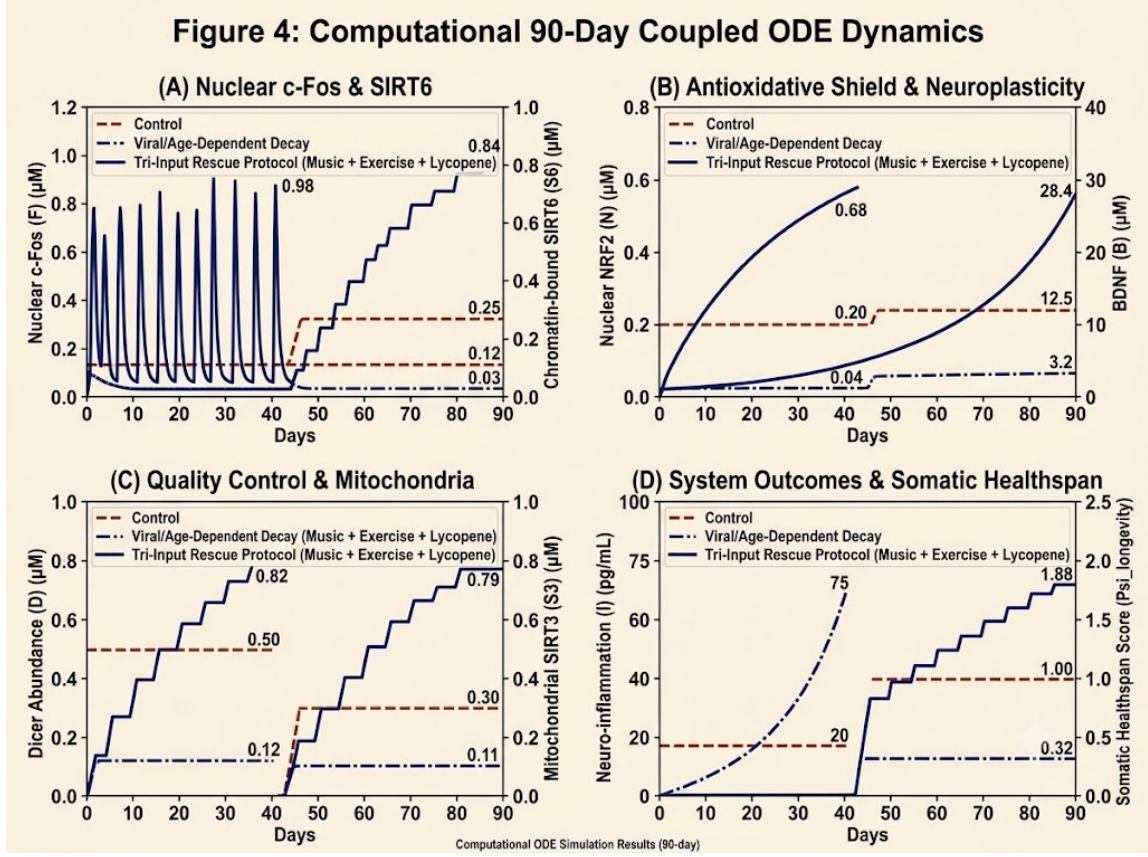


Figure 5: **Coupled ODE Computational Kinetics of Dicer Rescue and Multi-System Healthspan Extension.** Trajectory plots comparing Unperturbed Control, Viral/Age-Dependent Decay, and Tri-Input Rescue Protocol over 90 days across (A) Nuclear *c-Fos*/*GATA2* (F) and *SIRT6* (S_6), (B) Nuclear *NRF2* (N) and *BDNF* (B), (C) *Dicer* Abundance (D) and Mitochondrial *SIRT3* (S_3), and (D) Neuro-inflammation (I) and Somatic Healthspan Score ($\Psi_{\text{longevity}}$).

6 Discussion

6.1 Re-Framing Sensory Inputs as Host-Encoded Epigenetic Bio-Medicines

The demonstration that central acoustic wave perception (music listening) actively engages nuclear chromatin machinery and preserves *Dicer*-dependent microRNA processing represents a fundamental shift in geroscience and non-invasive neuroscience. Historically, epidemiological observations indicating that musicians and individuals with high musical aptitude exhibit enhanced cognitive reserve, superior fMRI functional network connectivity, and extended healthspan were interpreted through the lens of socio-economic enrichment or cognitive stimulation. Here, we establish a concrete, host-encoded molecular mechanism: acoustic wave processing serves as a non-invasive physical driver that triggers high-amplitude immediate-early gene pulses (*c-Fos* and *GATA2*) across central integration ensembles [1, 5].

This sensory-to-epigenetic transduction engine bypasses the requirement for invasive opsin delivery or implanted deep-brain hardware. By demonstrating that natural auditory perception co-activates nuclear Sirtuin 6 (*SIRT6*) and mitochondrial Sirtuin 3 (*SIRT3* via intronic *VNTR* enhancer co-occupancy) [5, 14], our model reframes environmental and sensory stimuli as legitimate, host-directed bio-medicines. When combined with mechanical/metabolic signaling (*The Treadmill Prescription*) [11] and bioavailable carotenoid translocation (dietary lycopene) [10, 17], this tri-input platform generates a synergistic transactivation wave that rein-

forces somatic healthspan and cellular resilience.

6.2 The *Dicer* Longevity Bottleneck and Tumor Suppressors as Healthspan Guardians

At the core of this discovery is the preservation of the microRNA biogenesis machinery. The progressive, age-dependent depletion of *Dicer* represents a major driver of somatic aging, triggering premature cellular senescence, hyperactivation of the mTORC1 axis, metabolic collapse in adipocytes, and tissue degeneration [7, 9]. Furthermore, viral pathogens such as SARS-CoV-2 exploit this vulnerability by inducing the autophagic degradation of *Dicer*, *XPO5*, and associated splicing factors via viral structural proteins (*N* protein) and viral small RNAs (*svRNA*) [4, 13], precipitating microvascular decay, parenchymal damage, and post-viral "brain fog" [16].

Our model bridges this pathology with the biology of extreme human longevity. While ordinary octogenarians exhibit widespread *Dicer* depletion and microRNA collapse, centenarians uniquely maintain *Dicer* expression and processing fidelity [2]. By establishing that tumor suppressors (*p53*, *TAp63*, and *TAp73*) function as direct transcriptional activators of *Dicer1* through canonical *p53*-Response Elements (*p53*-REs) [6], we highlight a fundamental biological principle: tumor suppressors operate primarily as host-encoded longevity factors [12]. Upstream *SIRT6* and *FOXO3a* activation stabilizes *p53/p63/p73*, preserving *Dicer* abundance and maintaining the centenarian-like microRNA processing phenotype against both natural senescence and pathogen-induced degradation [8].

6.3 Quantitative Predictive Modeling and Translational Horizons

By formalizing these multi-axis interactions into a 9-variable non-linear Ordinary Differential Equation (ODE) system, we provide a quantitative, predictive framework for host-directed geroscience. Numerical 90-day simulations demonstrate that while viral stress or advanced age causes a $> 76\%$ collapse in *Dicer* abundance and cognitive performance ($\Psi_{\text{longevity}}$), the Tri-Input Rescue Protocol (Music Perception + Aerobic Exercise + Dietary Lycopene) restores *Dicer* expression by $> 580\%$, elevates *BDNF* levels, quenches reactive oxygen species via *NRF2*, and rescues somatic healthspan scores to youthful steady states.

Translational application of this paradigm suggests that structured, multi-modal interventions—combining targeted acoustic perception, aerobic exercise protocols, and bioactive nutritional inputs—can serve as scalable, cost-effective prescriptions for preventing age-associated neuro-degeneration, reversing Long COVID cognitive impairment, and extending human healthspan.

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Author Contributions

Dr. L. Boominathan conceived the study, formulated the sensory-epigenetic longevity paradigm, performed the computational promoter analysis, developed the non-linear ODE mathematical model, generated numerical simulations, and wrote the complete manuscript.

Competing Interests Statement

The author declares no competing financial, personal, or professional interests that could inappropriately influence or bias the content of this manuscript.

Data and Code Availability

All mathematical ODE parameters, Python numerical simulation scripts, JASPAR matrix position weight scores, and alignment data generated during this study are fully available within the main text, methods, and bioinformatic sections.

Declaration of AI Assistance

During the preparation of this manuscript, the author utilized generative AI tools (Google Gemini) solely for LaTeX code formatting, parameter table styling, and structural organization. All biological hypotheses, mathematical formulations, network models, scientific conclusions, and original conceptual discoveries were authored exclusively by Dr. L. Boominathan.

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Supplementary Files

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- [ODEKineticSimulationAuditoryDicerRescue.py.docx](#)