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BIOHACKING LONGEVITY: GENOMIC AND EPIGENETIC MODULATION FOR PERSONALIZED NEUROFUNCTIONAL INTERVENTIONS

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Abstract: This paper organizes mechanistic evidence on functional longevity and cognitive preservation, focusing on pathways that connect bioenergetics, redox control, and mitochondrial quality. The SIRT1 FOXO mTOR AMPK axes, the Nrf2 HO-1 antioxidant response, PINK1 PRKN mitophagy, the BMAL1-mediated molecular clock, and the BDNF TrkB synaptic system are discussed. The selected literature describes convergent effects, such as induction of autophagy and mitophagy, modulation of reactive oxygen species, maintenance of endothelial junctions in the blood-brain barrier, support of mitochondrial biogenesis, and support of synaptic plasticity. Based on these mechanisms, the text outlines measures applicable in clinical practice and in a low-risk behavioral context, with objective monitoring and respect for experimental extrapolation limits. The final proposal is a decision roadmap that prioritizes safety, measurability, and individual stratification by integrating genomics, epigenetics, and neuroscience (Bin-Jumah et al., 2022; Loboda et al., 2016; Zhai et al., 2022; Choi et al., 2014; Navarro; Esteras, 2024; Guan; Chen; Dong, 2025; Tang et al., 2025; Sang et al., 2025; Toader et al., 2025; Csik et al., 2025).

Keywords: longevity biohacking; neurogenomics; Nrf2 HO-1; PINK1 PRKN; SIRT1 FOXO AMPK; BMAL1; BDNF TrkB.

Introduction

Functional longevity depends on the interaction between genetic variability, epigenetic regulation, and environmental contexts that modulate energy homeostasis, inflammation, and proteostasis. Recent evidence maps genes and pathways that influence lifespan extension and cognitive function maintenance, including SIRT1, FOXO, mTOR, AMPK, and antioxidant and mitochondrial quality control axes such as Nrf2/HO-1 and PINK1/PRKN (Bin-Jumah et al., 2022; Loboda et al., 2016). In the brain, the integration between mitochondrial metabolism, glial response, and synaptic plasticity, involving BDNF/TrkB, participates in trajectories of resilience or cognitive decline (Toader et al., 2025; Navarro; Esteras, 2024). This work organizes an interpretable framework of evidence-based biohacking to guide personalized interventions focused on longevity and brain health.

Methodology

Narrative literature review with targeted selection of original and review articles published between 2014 and 2025, prioritizing mechanisms tested in cellular and animal models, as well as syntheses with translational potential. The curation and textual organization stage was supported by artificial intelligence systems for screening references, checking internal consistency, and standardizing citations, while maintaining authorship, interpretation of findings, and editorial decisions under human responsibility. Sources include mappings of genes associated with longevity, epigenetic regulation by caloric restriction, Nrf2 HO-1 response, PINK1 PRKN mitophagy, BMAL-1-mediated circadian axes, and BDNF TrkB synaptic targets, with an emphasis on peer-reviewed works with DOI.

Environmental Regulation of Gene Pathways: Epigenetic Foundations for Personalized Longevity Strategies

The application of behavioral strategies based on molecular evidence provides a consistent foundation for interventions aimed at functional longevity. Recent studies demonstrate that pathways such as SIRT1, mTOR, and FOXO, associated with the regulation of aging, can be modulated by environmental variables, including caloric intake and metabolic rhythms. The coordinated activation of these pathways participates in the maintenance of energy homeostasis, induction of autophagy, and preservation of mitochondrial integrity, processes considered fundamental in attenuating senescent progression at the cellular level (Bin-Jumah et al., 2022).

To illustrate this process in an applied way, consider the hypothetical case of an individual with a genetic profile compatible with high expression of the SIRT1 pathway, but with dysregulated eating habits and chronically fragmented sleep. Despite favorable genetic potential, the absence of adequate environmental stimuli, such as controlled eating windows and cyclical exposure to fasting, reduces the effective activation of this pathway. In contrast, the introduction of nutritional protocols based on moderate caloric restriction, associated with the regularization of the circadian rhythm and physical activity, could reverse this situation. Environmental modulation would induce the functional activation of SIRT1, favoring autophagic processes and reducing inflammatory markers associated with premature mitochondrial senescence.

In addition, epigenetic evidence associated with caloric restriction indicates that such intervention acts on post-translational modifications and specific epigenomic marks. These changes directly influence the expression of aging-regulating genes, modulating factors associated with oxidative stress, cellular inflammation, and mitochondrial metabolism. As demonstrated by Zhai et al. (2022), caloric restriction promotes a cellular environment favorable to longevity, integrating autophagy and epigenetics as complementary axes of regulation. The consolidation of this evidence establishes an interpretable basis for functional biohacking, in which the integration of genomics, epigenetics, and environmental stimuli can be directed toward personalized protocols for extending healthy lifespan.

Redox-Regulatory Activation as a Conserved Mechanism of Cellular Defense

The Nrf2/HO-1 pathway is a conserved mechanism of cellular defense against oxidative stress, with coordinated induction of antioxidant, detoxifying, and inflammation-modulating genes. Under conditions of redox stress, Nrf2 stabilizes, migrates to the nucleus, and activates antioxidant response elements, promoting the expression of HO-1, NQO1, GCL, and other enzymes that limit damage to proteins, lipids, and DNA (Loboda et al., 2016). This dynamic sustains mitochondrial homeostasis and protects against programmed cell death, with implications for healthy aging.

The literature describes that sustained activation of Nrf2 is associated with greater tissue resilience and lower chronic inflammatory burden, relevant aspects in age-re-

lated diseases and strategies for extending healthy lifespan. HO-1, induced by Nrf2, degrades heme and generates biliverdin, bilirubin, and carbon monoxide at physiological levels, molecules with cytoprotective and anti-inflammatory effects, which contribute to reducing the progression of cumulative damage throughout life (Loboda et al., 2016).

In the context of longevity biohacking, this pathway offers an operational target for behavioral and nutritional interventions that reduce oxidative stress and preserve cellular adaptive capacity. The structuring of routines that stabilize energy balance, sleep, and physical activity, together with h nd nutritional protocols that avoid caloric excess and deficiencies, tends to favor the Nrf2/HO-1 axis and modulate inflammatory and oxidative damage markers in a functional and measurable way (Loboda et al., 2016).

Consider an adult with an irregular sleep routine, a diet rich in ultra-processed foods, and little exercise. In this scenario, cells deal with more "internal smoke" from free radicals, and the defense system can become overwhelmed. After organizing sleep schedules, adopting a diet based on real food, and practicing daily walking, the body begins to activate the cellular "defense button" more efficiently. In simple terms, the Nrf2 coordinator kicks in more regularly, turning on protective genes, and the HO-1 enzyme helps "clean up" toxic waste. The expected result is less silent inflammation and cells that age more slowly, which translates into more energy and better functionality over time (Loboda et al., 2016).

AMPK SIRT1 FOXO Integration: Antioxidant Architecture for Personalized Longevity Strategies

The AMPK SIRT1 FOXO pathway operates as a bioenergetic and antioxidant regulatory axis, activated in contexts of redox imbalance and energy depletion. AMPK activation promotes NAD+ increase, potentiates SIRT1, and, subsequently, FOXO deacetylation, with induction of antioxidant genes such as SOD and CAT, improvement of mitochondrial biogenesis via PGC-1α, and reduction of damage by reactive oxygen species. This functional arrangement increases metabolic efficiency, regulates autophagy, and limits apoptosis, forming a mechanistic basis for extending healthy lifespan and mitigating diseases associated with oxidative stress, including in neurodegenerative contexts. Together, the AMPK SIRT1 FOXO axis integrates energy homeostasis, inflammation control, and mitochondrial quality, making it a strategic target for molecularly based longevity interventions (Guan; Chen; Dong, 2025).

Consider a person with an irregular sleep routine, a high-calorie diet, and low physical activity. This scenario increases the production of free radicals and overloads the mitochondria. By adjusting eating windows with caloric moderation, organizing sleep, and incorporating daily walks, there is an energetic stimulus that activates AMPK, elevates SIRT1, and enables FOXO to turn on defense genes. In practical terms, the body improves "cellular cleaning" through autophagy, optimizes mitochondrial function, and reduces silent inflammation, which translates into greater functionality over

time, within physiological limits and with professional monitoring when necessary (Guan; Chen; Dong, 2025).

As an offshoot of longevity biohacking, protocols that combine adequate intensity exercise, caloric modulation without malnutrition, and a stable circadian routine tend to reinforce the AMPK SIRT1 FOXO pathway and its effects on mitochondrial quality, antioxidant defense, and control of pro-inflammatory pathways. The literature also indicates interfaces with Nrf2 and autophagy mechanisms, suggesting synergy between redox regulation and proteostatic maintenance, with particular relevance to brain aging and cognitive performance preservation, provided they are anchored in evidence and with individualized assessment (Guan; Chen; Dong, 2025).

Nrf2 in the Central Nervous System: Redox Regulation, Mitochondria, and Neuroinflammation for Functional Longevity

Nrf2–Keap1 signaling in the brain acts as a multi-target cytoprotective axis that coordinates energy metabolism, antioxidant defense, and inflammatory control in different cell types, with greater activity in astrocytes and microglia than in neurons. The nuclear stabilization of Nrf2 induces antioxidant response and detoxification genes, sustains mitochondrial bioenergetics, and modulates pro-inflammatory pathways, including interaction with NF-κB and the NLRP3 inflammasome, configuring a relevant mechanism for maintaining neural homeostasis and functional preservation throughout aging (Navarro; Esteras, 2024).

An adult with an irregular routine, a diet rich in ultra-processed foods, and shortened sleep tends to accumulate free radicals in the brain, which puts pressure on mitochondria and activates microglia in a pro-inflammatory manner. By organizing sleep schedules, adjusting calories to demand, and practicing regular physical activity, the oxidative load is reduced and the efficiency of internal defenses is favored. In functional terms, pathways regulated by Nrf2 in astrocytes and microglia begin to better support neurons with greater availability of NADPH, glutathione, and control of inflammatory signaling, which is associated with greater neural metabolic resilience (Navarro; Esteras, 2024).

As a translational implication, the literature describes the pharmacological activation of Nrf2 in neurological scenarios, including with clinically approved inducers, in addition to effects on mitochondrial biogenesis, neuronal glucose metabolism, and resistance to ferroptosis in glia. These results reinforce the usefulness of the Nrf2 axis as a target for research at the neuroscience-genomics interface of longevity, with potential for personalized protocols that integrate behavioral habits and, when indicated, validated therapeutic strategies (Navarro; Esteras, 2024).

SMAD3 and PINK1 in mitophagy: transcriptional regulation and implications for neurofunctional longevity

Recent evidence describes that mitochondrial stress with depolarization stimulates PINK1 transcription and that SMAD3 acts as a positive nuclear factor for this gene

(Tang et al., 2025). In cellular models, inhibition of mRNA synthesis reduced PINK1, which supports active transcriptional control during mitochondrial aggression. ChIP and reporter experiments indicated SMAD3-responsive elements in the PINK1 promoter, while SMAD3 loss of function decreased PINK1 and p-ubiquitin S65 and compromised stages of mitophagy, such as Parkin translocation, mitochondrial protein degradation, and mtDNA clearance. The study further demonstrates that PINK1 directly phosphorylates SMAD3 at S423 S425 and that both form a positive feedback loop that favors mitophagy and confers a pro-survival signal under mitochondrial stress. This effect is independent of the canonical TGFβ pathway with SMAD2 SMAD4, reinforcing a non-canonical role for SMAD3 in the transcriptional regulation of PINK1 and in mitochondrial homeostasis with relevance to neurodegenerative diseases (Tang et al., 2025).

The integration of this axis with longevity biohacking can be interpreted from the perspective of mitochondrial quality control in neural tissues. The positivity of the SMAD3 PINK1 loop suggests that conditions that minimize chronic mitochondrial damage and preserve autophagic capacity tend to sustain the efficiency of the system, which is in line with strategies aimed at brain health and functional lifespan. The study also contextualizes interactions with known regulators of cellular longevity, such as FOXO3, and discusses the role of SMAD3 in resilience to mitochondrial stress-induced apoptosis, which positions the axis as a target for translational research in neuroscience and applied genomics.

Imagine a person with a family history of movement disorders who works shifts, sleeps little, and maintains an irregular diet. This pattern increases stress on the mitochondria of neurons. By reorganizing sleep into stable schedules, adjusting diet to avoid caloric spikes, and incorporating regular physical activity, the pressure on the mitochondria is reduced. In simple terms, the internal system that identifies damaged mitochondria is better able to trigger the "recall" of these parts because the dialogue between SMAD3 and PINK1 becomes more efficient. This means less accumulation of cellular waste and greater adaptability of the brain over time, within physiological limits and with professional monitoring when necessary.

BMAL1–SIRT1/PGC-1: bioenergetic and inflammatory modulation with implications for tissue longevity

In in vitro models of nucleus pulposus cells, BMAL1 overexpression activated the SIRT1/PGC-1α pathway, elevated PINK1/Parkin-dependent mitophagy markers, and reduced oxidative stress, inflammation, apoptosis, and senescence; knockdown of BMAL1 produced the opposite effect, and co-inhibition of SIRT1 or PINK1 attenuated the protective effects, indicating functional mediation of these axes (Sang et al., 2025). These results describe an operational mechanism for preserving mitochondrial quality and cellular activity, with a direct impact on catabolic processes in tissues subject to overload and biological aging. The solution proposed by the study is clear in mechanistic terms: increase BMAL1, when

feasible, and sustain the SIRT1/PGC-1α loop to mitigate ROS, modulate cytokines, and maintain mitochondrial turnover, bearing in mind that the evidence is bench-based and requires validation in animal models and clinical contexts before therapeutic extrapolations (Sang et al., 2025). In terms of future translational application, two vectors are outlined: 1) interventions that preserve circadian alignment, given the central role of BMAL1 in the molecular clock; 2) strategies that safely support SIRT1/PGC-1α and mitophagy, with individualized design, to reduce tissue vulnerability to oxidative and inflammatory damage over time (Sang et al., 2025).

A professional who spends long hours sitting, with variable sleep and eating schedules, reports frequent low back pain. This pattern increases stress on the intervertebral disc cells. By setting a regular sleep window, organizing meal times, and including daily walks, they reduce metabolic stress peaks and improve the cellular environment. In plain language, the cells' "power plants" function with fewer free radicals, the recycling of defective mitochondria occurs more efficiently, and inflammatory signals decrease. The study suggests that biological pathways linked to BMAL1 and the SIRT1/PGC-1α pathway participate in this protection at the cellular level, which helps to understand why consistent habits can sustain more resilient tissues over time, always with professional monitoring when there is persistent pain or established disease (Sang et al., 2025).

PINK1 and PGC-1 in mitochondrial fatty acid oxidation: implications for dementia and diabetes

The study demonstrates that PINK1 and PGC-1α proteins are reduced in the hippocampus of brains with Alzheimer's disease and in models of diabetes, a condition associated with mitochondrial dysfunction, increased oxidative stress, and a decrease in key β-oxidation enzymes, such as ACADVL and HADHA. In cells exposed to hydrogen peroxide, the expression of PINK1 and the 35 kDa isoform of PGC-1α decreased and was preserved with N-acetylcysteine, suggesting sensitivity of the axis to redox control. In lines overexpressing PGC-1α, PINK1 silencing increased lipid droplet accumulation and reduced fatty acid oxidation capacity as measured by oxygen consumption in the presence of palmitate, an effect blocked by the CPT-1 inhibitor, confirming the direct involvement of mitochondrial β-oxidation. The authors propose a cooperative role for PINK1 and PGC-1α in maintaining fatty acid oxidation and protecting against lipotoxicity, with relevance to neurodegenerative and metabolic states. The practical translation indicated by the study itself is clear in mechanistic terms: reducing oxidative stress and sustaining PGC-1α function tend to preserve mitochondrial quality and β-oxidation; any clinical extrapolation requires further validation, but the general vector points to strategies that minimize lipid overload, stabilize the redox environment, and support neuronal bioenergetics.

Consider a person with a family history of dementia and irregular glycemic control, who eats high-fat meals and has a sedentary routine. This scenario increases the "bottle-

neck" of fat within cells and puts pressure on the mitochondria. By organizing meal times, reducing excess calories, prioritizing real food, and including daily walks, the cell better handles fats as an energy source. In simple terms, the PINK1 and PGC-1α "pair" can operate more efficiently, the cellular power plant burns fuel better, less waste is left over, and fat accumulation inside cells is reduced, which helps protect the brain over time, within physiological limits and with professional monitoring when disease is present.

Blood-brain barrier and neurovascular coupling in aging: endothelial senescence as a vascular and cognitive driver

In a murine model, aging promotes early and marked senescence in endothelial cells of the cerebral microcirculation, associated with three key changes: worsening neurovascular coupling, capillary rarefaction, and increased blood-brain barrier permeability. Targeted elimination of senescent cells, either genetically in the p16-3MR model with ganciclovir or by pharmacological senolytic approach with navitoclax, restored neurovascular coupling responses, increased microvascular density, reduced barrier disruption, and improved spatial memory performance. The analysis suggests a window of greater benefit in middle age, indicating that senescent endothelial burden is an early determinant of neurovascular dysfunction and age-related cognitive decline, with direct implications for the prevention of vascular cognitive impairment. This is robust preclinical evidence in mice, with translational relevance for strategies aimed at reducing the endothelial SASP phenotype and preserving barrier integrity and fine cerebral perfusion.

Consider a middle-aged person with poorly controlled hypertension, irregular sleep, and a sedentary lifestyle. This combination increases stress on the cerebral vessels, promotes premature aging of the endothelium, and leaves the blood-brain barrier more vulnerable. By stabilizing blood pressure with medical supervision, organizing sleep schedules, and including daily walking, the inflammatory pressure on the capillaries is reduced. In functional terms, the vessels respond better to signals from the brain, the barrier becomes less "leaky," and the delivery of oxygen and nutrients becomes more efficient, which protects memory and attention over time, always respecting individual limits and professional guidance. This illustration is consistent with the logic observed in animal studies, which showed neurovascular improvement when the burden of endothelial senescence is reduced.

BDNF and TrkB in cognitive longevity: from synaptic plasticity to translational application

The review describes BDNF as a central target for sustaining synaptic plasticity, cognitive resilience, and neuronal survival, with implications from development to neurodegeneration. The work maps BDNF gene and epigenetic regulation, the roles of proBDNF and mBDNF, and signaling via TrkB integrated with MAPK/ERK, PI3K/Akt, and PLC-γ pathways, highlighting both LTP and LTD as bases for memory and adaptation. From a translational perspective, it presents three solution vectors: biomarkers and panels combining BDNF

with tau and Aβ for early detection; therapeutic strategies that bypass the blood-brain barrier, such as mRNA in lipid nanoparticles, small molecule TrkB agonists, and CRISPR-dCas9 epigenetic editing; and lifestyle interventions that elevate BDNF and promote plasticity. The practical proposal, in line with the article, is to structure protocols that combine multimodal BDNF monitoring, pharmacological intervention when validated, and a standardized behavioral core with regular aerobic exercise and a polyphenol-rich diet, both associated with increased BDNF and cognitive performance gains, always with clinical validation and respect for individual profiles.

A middle-aged person reports memory lapses and a sedentary routine. The initial plan includes moderate walking five times a week and dietary adjustments with the inclusion of natural sources of polyphenols. In simple terms, these measures increase BDNF availability, strengthen connections between neurons, and improve synaptic "conversation." Follow-up laboratory tests and, when indicated, biomarker panels help monitor response. In specific scenarios and under research protocols or future clinical guidelines, TrkB modulators or targeted delivery approaches of BDNF itself may be used. The goal is to keep the brain more adaptable, with memory and attention preserved over time.

Discussion

The literature converges on an operational core in which low-complexity behavioral interventions translate into modulation of longevity pathways. Safe caloric restrictions and stable eating windows are associated with the activation of AMPK and SIRT1, the deacetylation of FOXO, increased autophagy, and the reduction of ROS, with effects on mitochondrial integrity and the attenuation of inflammatory markers (Zhai et al., 2022; Guan; Chen; Dong, 2025). In parallel, Nrf2 activation and HO-1 induction stabilize the baseline antioxidant response, reinforce detoxification systems, and preserve endothelial junction proteins, with an impact on the neurovascular axis and the blood-brain barrier (Loboda et al., 2016; Navarro; Esteras, 2024; Csik et al., 2025). The mitochondrial dimension occupies a central position. The PINK1/PRKN circuit is crucial for efficient mitophagy, and there is evidence of regulatory loops that include SMAD3 under mitochondrial stress, strengthening the selective removal of dysfunctional organelles and the maintenance of neuronal bioenergetics (Tang et al., 2025). The metabolic interface between fatty acid oxidation and synaptic function indicates cooperation between PINK1 and PGC-1α, with data linking bioenergetic dysregulation to dementia risk and metabolic states such as diabetes (Choi et al., 2014). In tissues susceptible to degeneration, the biological chronotype influences SIRT1/PGC-1α pathways and BMAL1-regulated mitophagy, sustaining mitochondrial quality and reducing pro-inflammatory and cellular senescence signals, although translational evidence requires further clinical validation (Sang et al., 2025).

At the synaptic level, BDNF/TrkB remains a critical axis for LTP, LTD, and neuronal survival, with translational proposals ranging from TrkB agonists to targeted delivery platforms, as well as behavioral interventions related to aerobic exercise and routine organization that elevate BDNF in cognitive risk scenarios (Toader et al., 2025).

The synthesis of these results supports an interpretable biohacking model in which personalized protocols combine nutrition with caloric moderation and nutritional density, regular physical activity, circadian hygiene, and, when relevant, molecular targets with preclinical evidence, always under risk-benefit assessment and monitoring of clinical outcomes. Important limitations remain, such as the predominance of experimental studies and heterogeneity of protocols, which require pragmatic trials and integrative biomarkers to guide decisions.

The reviewed results support that low-risk behavioral measures and objective monitoring can modulate pathways linked to cellular longevity and cognitive performance, including SIRT1 FOXO AMPK regulation, Nrf2 HO-1 induction, PINK1 PRKN mitophagy maintenance, BMAL1-mediated circadian synchronization, and BDNF TrkB support. Inferences remain subject to clinical validation and individual stratification.

Final considerations

The integration of genomics, epigenetics, and neuroscience provides a functional basis for longevity strategies focused on maintaining adaptive capacity and cognitive protection. The reviewed evidence indicates that systematic and monitorable interventions focused on AMPK/SIRT1/FOXO modulation, Nrf2/HO-1 activation, PINK1/PRKN mitophagy efficiency, BMAL1-mediated circadian organization, and BDNF/TrkB axis support represent a plausible path to extending healthspan and neurofunctional performance. Clinical application must respect extrapolation limits, incorporate risk stratification, and be supported by professional monitoring, with priority given to safety, measurability, and reproducibility. Controlled clinical studies and multimodal biomarker platforms are the next steps in consolidating personalized longevity biohacking protocols. We propose a decision protocol that integrates clinical screening, definition of measurable goals, safety monitoring, and periodic review of evidence. The priority is to avoid extrapolations, document effects, and incorporate viable biomarkers as they become available.

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