

Exercise-Induced Mitochondrial Stress and cGAS-STING Signaling in Healthy Aging

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ABSTRACT

Purpose: This review aims to examine the potential relationship between exercise-induced mitochondrial adaptation, mitochondrial DNA (mtDNA) homeostasis, and cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling during brain aging. Particular emphasis is placed on the role of mitochondrial quality control and the proposed mitochondrial stress-resolution threshold as a potential mechanism linking exercise with healthy brain aging and longevity.

Method: A focused narrative review was conducted by evaluating human, animal, and in vitro/cellular studies, together with relevant review articles, addressing exercise-induced mitochondrial adaptation, mitochondrial quality control, mtDNA homeostasis, cGAS-STING signaling, neuroinflammation, and brain aging. Evidence from different biological levels was narratively synthesized to examine the potential mechanistic relationship between exercise-induced mitochondrial stress and age-related innate immune activation.

Results: Exercise-induced mitochondrial stress can promote mitochondrial biogenesis, turnover, antioxidant defense, and mitochondrial resilience. Aging may impair these adaptive processes and increase mitochondrial dysfunction and mtDNA dysregulation. Cytosolic mtDNA can activate cGAS-STING signaling, while emerging evidence links this pathway to microglial activation and neuroinflammation during brain aging. However, direct evidence connecting exercise with modulation of the brain mtDNA-cGAS-STING axis remains limited.

Conclusion: Exercise may influence age-related neuroinflammation primarily by improving mitochondrial quality control and maintaining mtDNA homeostasis rather than through direct suppression of cGAS-STING signaling. The proposed mitochondrial stress-resolution threshold provides a testable framework linking exercise dose, mitochondrial adaptation, mtDNA regulation, innate immune signaling, and healthy brain aging.

Keywords: Exercise, Aging, Mitochondrial Dysfunction, Mitochondrial DNA, cGAS-STING, Neuroinflammation.

ÖZET

Sağlıklı Yaşlanmada Egzersize Bağlı Mitokondriyal Stres ve cGAS-STING Sinyalizasyonu

Amaç: Bu derlemenin amacı, egzersize bağlı mitokondriyal adaptasyon, mitokondriyal DNA (mtDNA) homeostazı ve beyin yaşlanması sırasında siklik GMP-AMP sentaz–interferon genlerinin (cGAS-STING) uyarıcısı sinyal yolları arasındaki potansiyel ilişkiyi incelemektir. Özellikle, mitokondriyal kalite kontrolünün ve önerilen mitokondriyal stres-çözülme eşiğinin egzersiz ile sağlıklı beyin yaşlanması ve uzun yaşam arasındaki potansiyel mekanizmadaki rolü ele alınmıştır.

Yöntem: Egzersize bağlı mitokondriyal adaptasyon, mitokondriyal kalite kontrolü, mtDNA homeostazı, cGAS-STING sinyalizasyonu, nöroinflamasyon ve beyin yaşlanmasını ele alan insan, hayvan ve in vitro/hücrel çalışmalar ile ilgili derleme makaleleri değerlendirilerek odaklanmış bir derleme gerçekleştirilmiştir. Farklı biyolojik düzeylerden elde edilen kanıtlar,

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egzersize bağı mitokondriyal stres ile yaşa bağı doğuştan bağışıklık aktivasyonu arasındaki potansiyel mekanistik ilişkiyi incelemek amacıyla sentezlenmiştir.

Bulgular: Egzersize bağı mitokondriyal stres; mitokondriyal biyogenez, mitokondriyal dönüşüm, antioksidan savunma ve mitokondriyal dayanıklılığı destekleyebilir. Yaşlanma bu adaptif süreçleri bozarak mitokondriyal disfonksiyon ve mtDNA düzensizliğini artırabilir. Sitozolik mtDNA, cGAS-STING sinyal yolunu aktive edebilirken, gelişmekte olan kanıtlar bu yolun beyin yaşlanması sırasında mikrogliyal aktivasyon ve nöroinflamasyon ile ilişkili olduğunu göstermektedir. Bununla birlikte, egzersizin beyindeki mtDNA-cGAS-STING eksenini modüle ettiğini doğrudan gösteren kanıtlar halen sınırlıdır.

Sonuç: Egzersiz, cGAS-STING sinyalizasyonunu doğrudan baskılamaktan ziyade mitokondriyal kalite kontrolünü iyileştirerek ve mtDNA homeostazını koruyarak yaşlanmaya bağı nöroinflamasyonu etkileyebilir. Önerilen mitokondriyal stres-çözölme eşiği modeli; egzersiz dozu, mitokondriyal adaptasyon, mtDNA düzenlenmesi, doğuştan bağışıklık sinyalizasyonu ve sağlıklı beyin yaşlanması arasındaki ilişkiyi açıklamak için test edilebilir bir çerçeve sunmaktadır.

Anahtar Kelimeler: Egzersiz, Yaşlanma, Mitokondriyal Disfonksiyon, Mitokondriyal DNA, cGAS-STING, Nöroinflamasyon.

INTRODUCTION

Aging is accompanied by progressive loss of physiological resilience and an increasing susceptibility to metabolic, inflammatory, and neurological dysfunction (Jurcau et al., 2024; Wu et al., 2026). Mitochondrial dysfunction is a central feature of this process, characterized by impaired energy metabolism, altered mitochondrial turnover, oxidative imbalance, and reduced capacity to maintain cellular homeostasis (Zhu et al., 2026). These changes are particularly relevant to the brain, where high energetic demands make neuronal and glial cells highly dependent on mitochondrial integrity (Rim et al., 2024; Steffan et al., 2025). Persistent mitochondrial dysfunction may therefore contribute to neuroinflammation and age-related decline in brain function (Klemmensen et al., 2024; Li et al., 2026).

Exercise is one of the most effective physiological interventions for maintaining metabolic and functional health during aging (Kong et al., 2025; Pradeepkiran et al., 2025). Regular physical activity promotes mitochondrial biogenesis, improves oxidative capacity, enhances antioxidant defenses, and stimulates mitochondrial quality-control mechanisms (Picca et al., 2023). Importantly, exercise itself represents a controlled physiological stressor (Karagianni & Bazopoulou, 2024; Szechyńska-Hebda et al., 2022). Transient increases in metabolic demand and reactive oxygen species can activate adaptive responses that improve subsequent stress tolerance (Bartman et al., 2024; Bondy, 2024). Thus, the biological effects of exercise depend not simply on the presence of mitochondrial stress but on the capacity of tissues to resolve that stress and convert it into adaptation (Broome et al., 2024; Cai et al., 2026).

Mitochondrial stress may also influence inflammatory signaling through effects on mtDNA homeostasis (Maldonado et al., 2023; Zhu et al., 2025). Damage to mitochondria or impaired mitochondrial quality control can increase mtDNA damage, release, or mislocalization (Algieri et al., 2025; Ma et al., 2025). Cytosolic mtDNA can act as an endogenous danger signal and activate the cGAS-STING pathway (Cai et al., 2026). Activation of this pathway can promote downstream TBK1/IRF3 and NF- κ B signaling and contribute to inflammatory responses (Li et al., 2025). In the aging brain, this mechanism may be particularly relevant because mitochondrial dysfunction and altered microglial activity can coexist with chronic low-grade neuroinflammation (Suk, 2026). Experimental evidence has linked mitochondrial perturbation, cytosolic DNA accumulation, and cGAS-STING activation with inflammatory and age-related changes in microglia (Rim et al., 2024).

The relationship between exercise and this pathway, however, remains incompletely defined. Exercise should not necessarily be considered a direct inhibitor of cGAS-STING signaling (Decout et al., 2021; Zhang & Zhang, 2025). Rather, repeated exercise may modify the upstream mitochondrial environment by improving mitochondrial quality control, antioxidant capacity, and the removal of damaged organelles (Lippi et al., 2022; Maciel et al., 2026; Slavin et al., 2022). These adaptations could reduce the persistence of mtDNA-associated danger signals and thereby influence the conditions under which innate immune signaling is activated (Jiménez-Loygorri et al., 2024; Newman & Shadel, 2023). Current evidence supports a biologically plausible relationship between exercise, mitochondrial adaptation, and cGAS-STING signaling, but direct evidence demonstrating a causal exercise-cGAS-STING pathway in the aging brain remains limited (Lim et al., 2022; Ma et al., 2026).

Accordingly, this review examines the emerging relationship between exercise-induced mitochondrial stress, mtDNA homeostasis, cGAS-STING signaling, and healthy brain aging. Particular emphasis is placed on mitochondrial quality control and the proposed concept of a mitochondrial stress-resolution threshold. Here, the term “mitochondrial stress-resolution threshold” is used as a conceptual framework to describe the point at which exercise-induced mitochondrial stress may exceed the capacity of mitochondrial quality-control and recovery mechanisms to restore cellular homeostasis. Importantly, this term does not refer to a defined or experimentally established biological threshold with a fixed quantitative value. Rather, it represents a hypothesis-generating and testable framework based on the premise that the biological consequences of exercise-induced mitochondrial stress depend on the balance between stress magnitude, mitochondrial resilience, and recovery capacity. Within this

framework, appropriately dosed exercise may promote adaptive mitochondrial remodeling, whereas persistent or insufficiently resolved mitochondrial stress may favor mtDNA-dependent inflammatory signaling (Burtscher et al., 2023). This framework may provide a mechanistic perspective for understanding how exercise contributes to healthy longevity and preservation of neurological function.

METHODS

Research Design

This review examines the relationship between exercise, mitochondrial stress, mtDNA homeostasis, cGAS-STING signaling, and aging, with particular emphasis on brain aging and neuroinflammation. This review was designed as a focused narrative review integrating evidence from human, animal, and in vitro studies, together with relevant mechanistic and review literature. This approach was selected because the proposed exercise-mitochondrial-mtDNA-cGAS-STING relationship involves multiple biological levels that cannot be adequately addressed by a single experimental model.

Literature Search

Relevant literature was identified through searches of PubMed, Web of Science, Scopus, and Google Scholar. The search was conducted on 25 August 2026 and was restricted to publications published between January 2000 and July 2026. No language restriction was applied. The search strategy was developed around four core concepts: exercise, mitochondrial stress and adaptation, mitochondrial quality control and mtDNA homeostasis, and cGAS-STING signaling in aging and brain inflammation. The search strategy combined terms related to these concepts, including “exercise”, “physical activity”, “mitochondrial stress”, “mitochondrial dysfunction”, “mitochondrial adaptation”, “mitophagy”, “mitochondrial DNA”, “mtDNA”, “cGAS”, “STING”, “cGAS-STING”, “aging”, “brain aging”, “neuroinflammation” and “microglia”. Database-specific combinations of these terms were adapted to the search interface and indexing structure of each database. Original research articles and relevant review articles addressing exercise-induced mitochondrial adaptation, mitochondrial quality control, mtDNA-dependent innate immune signaling, neuroinflammation, and healthy aging were considered.

Study Selection and Eligibility Criteria

Studies were considered eligible when they addressed at least one of the major mechanistic components of the review, including exercise-induced mitochondrial stress or adaptation, mitochondrial quality control, mtDNA homeostasis or release, cGAS-STING signaling, neuroinflammation, or brain aging. Human studies were considered particularly relevant for evaluating the physiological relevance and applicability of exercise-associated mitochondrial adaptations. Animal studies were included to investigate tissue- and organ-level mechanisms, particularly mitochondrial responses in the aging brain. In vitro and cellular studies were considered when they provided mechanistic evidence linking mitochondrial perturbation, mtDNA release or mislocalization, and cGAS-STING activation. Relevant review articles were included to provide conceptual and mechanistic context and to identify key primary studies.

Studies were excluded when they were unrelated to the main topics of the review or did not provide information relevant to the proposed mechanistic framework. Studies were also excluded when they did not provide sufficient scientific information relevant to exercise, mitochondrial biology, mtDNA-dependent innate immune signaling, aging, or neuroinflammation. Duplicate records identified across databases were manually removed before the final selection of relevant studies.

Evidence Classification and Synthesis

Evidence was interpreted according to the biological level and type of evidence provided by each study. Human studies were considered primarily for evidence of physiological relevance and exercise-associated mitochondrial adaptations, whereas animal studies were used to evaluate tissue-specific and organ-level mechanisms that cannot be readily assessed in humans. In vitro and cellular studies were considered primarily as mechanistic evidence for molecular interactions involving mitochondrial perturbation, mtDNA homeostasis, and cGAS-STING signaling. Review articles were used to provide broader conceptual and mechanistic context but were not treated as equivalent to primary experimental evidence.

The relevance of individual studies was assessed according to their directness to the central research question, biological model, experimental design, and ability to inform the proposed mechanistic relationship. Particular attention was given to studies that directly

examined mitochondrial function or quality control, mtDNA localization or release, cGAS-STING signaling, or exercise-related adaptations during aging. Evidence was interpreted according to the strength and directness of the available findings, and mechanistic inferences were not considered equivalent to direct causal evidence.

The literature was narratively synthesized according to four main themes: exercise-induced mitochondrial stress and adaptation; mtDNA-cGAS-STING signaling in aging and brain inflammation; exercise-related mitochondrial quality control and brain aging; and the relationship between exercise dose, aging, and mitochondrial stress resolution. Particular attention was given to distinguishing established experimental evidence from emerging mechanistic hypotheses. Because this review aims to integrate mechanistic evidence rather than quantitatively estimate treatment effects, no meta-analysis was performed.

RESULTS

Exercise-Induced Mitochondrial Stress and Adaptation

Exercise increases mitochondrial energy demand and transiently alters redox and metabolic homeostasis (Flensted-Jensen et al., 2026). These changes can increase reactive oxygen species production and activate cellular signaling pathways involved in antioxidant defense, mitochondrial biogenesis, and metabolic adaptation (Wang et al., 2023). Therefore, exercise-induced oxidative and metabolic stress should not be interpreted solely as cellular damage. When appropriately regulated, transient stress can function as a physiological stimulus that enhances mitochondrial resilience (Gorgori-Gonzalez et al., 2026).

Repeated exercise promotes mitochondrial remodeling through coordinated changes in mitochondrial biogenesis, turnover, and quality control (Xu et al., 2025). These adaptations can improve oxidative capacity and increase the ability of tissues to tolerate subsequent metabolic challenges (Alizadeh Pahlavani et al., 2022). Representative studies examining exercise-induced mitochondrial adaptations during aging are summarized in Table 1. The adaptive response, however, depends on exercise intensity, duration, frequency, training status, and recovery (Militello et al., 2024). Insufficient recovery or excessive exercise may prolong mitochondrial stress and reduce the capacity to restore cellular homeostasis.

This distinction is particularly important during aging (Campos et al., 2023). Age-associated alterations in mitochondrial turnover, mitophagy, antioxidant defense, and

mitochondrial genome maintenance may reduce the capacity to resolve exercise-induced mitochondrial perturbations. Consequently, the same exercise stimulus may produce different biological responses depending on the pre-existing mitochondrial state of the individual (Cai et al., 2026). The current evidence therefore supports exercise as a hormetic stimulus in which the physiological benefit is determined by the balance between transient stress and subsequent adaptation rather than by stress avoidance (Wang et al., 2023).

These observations provide an important basis for considering mtDNA-dependent innate immune signaling. When mitochondrial stress is effectively resolved, improved mitochondrial quality control may limit the persistence of damaged mitochondrial components (Zhang & Zhang, 2025). Conversely, prolonged mitochondrial dysfunction may increase mtDNA damage or mislocalization and create conditions favorable for activation of cytosolic DNA-sensing pathways. Thus, mitochondrial adaptation represents a potential upstream determinant of whether exercise-associated stress remains adaptive or contributes to persistent inflammatory signaling (Li et al., 2026).

Table 1. Representative experimental and human studies examining exercise-related mitochondrial adaptations in the context of aging

Study	Model / population	Exercise intervention	Main mitochondrial finding	Relevance to aging
(Menshikova et al., 2006)	Older men and women (mean age ≈67 years)	Exercise training	Increased skeletal-muscle mitochondrial content, reflected by increases in cardiolipin and mtDNA, together with increased electron transport chain activity, including succinate oxidase and NADH oxidase activity.	Demonstrates that older human skeletal muscle retains substantial capacity for mitochondrial biogenesis and functional adaptation to exercise.
(Konopka et al., 2014)	Young men (≈20 years) and older men (≈74 years)	12-week aerobic exercise training	Increased markers of mitochondrial biogenesis, including PGC-1 α , citrate synthase, β -HAD, SDH and COXIV, together with increased MFN1, MFN2 and FIS1 in both age groups.	Indicates that healthy aging does not abolish exercise-induced mitochondrial biogenesis or remodeling of mitochondrial dynamics in skeletal muscle.
(Wyckelsma et al., 2017)	Young and older adults	12-week high-intensity training	Older adults showed a robust increase in mitochondrial content, including increased citrate synthase activity, COXIV and NDUFA9, as well as increases in mitochondrial respiratory-chain complexes.	Demonstrates that older skeletal muscle can undergo substantial mitochondrial remodeling following high-intensity exercise despite age-related alterations in mitochondrial dynamics proteins.
(Chr�is et al., 2020)	Older sedentary men and	6-week supervised HIIT, 3	HIIT increased citrate synthase activity and MnSOD and complex I–V protein content in	Supports exercise-induced increases in mitochondrial content in

	women (n=22)	days/week	both sexes. Coupled and uncoupled mitochondrial respiratory capacity increased only in men.	older adults, while indicating that some functional adaptations may differ according to sex.
(Gusdon et al., 2017)	Aged mice	Exercise training	Exercise increased complex I-linked mitochondrial respiration and DRP1 protein expression in the brain. Mitochondrial protein content and markers of mitochondrial biogenesis, including PGC-1 α and TFAM, were not increased.	Provides evidence that exercise can improve brain mitochondrial function in aged animals through changes in electron transport chain function and mitochondrial dynamics, without necessarily increasing mitochondrial biogenesis.
(Luo et al., 2017)	Aged male Sprague-Dawley rats (16–18 months)	10-week swimming exercise	Exercise reduced oxidative stress and improved mitochondrial quality control in the hippocampus, with increased mitochondrial biogenesis, mitochondrial fusion and fission, and autophagy/mitophagy.	Directly links long-term exercise with preservation of hippocampal mitochondrial quality control and attenuation of age-related cognitive and mitochondrial alterations.
(Mesquita et al., 2022)	Female Lewis rats: young and middle-aged	Long-term voluntary physical activity	Physical activity increased cortical complex IV activity but did not alter mitochondrial complex protein content. Cortical carbonyl levels were also reduced, whereas several mitochondrial and redox markers remained unchanged.	Suggests that long-term physical activity can enhance specific aspects of cortical mitochondrial function and reduce oxidative protein damage, while overall brain mitochondrial responses to aging and activity may be region- and marker-specific.

mtDNA-cGAS-STING Signaling in Aging and Brain Inflammation

Mitochondrial dysfunction can contribute to inflammation through the release or mislocalization of mtDNA (Kim et al., 2023). Damaged mitochondria and impaired mitochondrial quality control may increase the availability of mtDNA in the cytosol, where it can function as an endogenous danger signal (Guilbaud et al., 2024). Cytosolic DNA is recognized by cGAS, leading to production of STING (Quan et al., 2025). Downstream signaling through TBK1, IRF3, and NF- κ B can promote interferon and pro-inflammatory responses (Wei et al., 2025). Representative studies investigating the relationship between mitochondrial dysfunction, mtDNA, and cGAS-STING signaling during aging are summarized in Table 2.

This mechanism may become increasingly relevant during aging because mitochondrial quality control progressively deteriorates (Salminen et al., 2025). Impaired mitophagy, altered mitochondrial dynamics, oxidative damage, and reduced mitochondrial

turnover may increase the persistence of dysfunctional mitochondria and mtDNA-associated signals (Izquierdo, 2024). In this context, cGAS-STING activation may provide a molecular link between mitochondrial dysfunction and chronic low grade inflammation (Zhou et al., 2025).

The brain is particularly vulnerable to this process because of its high energetic requirements (Ma et al., 2026). Microglia, as the principal innate immune cells of the central nervous system, can respond to mitochondrial and DNA-derived danger signals and contribute to neuroinflammatory responses. Experimental evidence indicates that mitochondrial perturbation and cytosolic DNA accumulation can activate cGAS-STING signaling in aged microglia and are associated with inflammatory phenotypes, neurodegeneration, and cognitive decline (Quan et al., 2025).

Importantly, cGAS-STING signaling should not be considered exclusively pathological (Salminen et al., 2025). Its physiological activity contributes to innate immune surveillance, and experimental findings indicate that complete loss of STING activity may also produce adverse neurological effects under some conditions. The biological consequences therefore appear to depend on cellular context, signaling intensity, and duration (Salminen et al., 2025; Wen et al., 2026). This distinction is relevant to exercise because the objective of exercise-induced adaptation may not be complete suppression of cGAS-STING signaling, but rather maintenance of an appropriate balance between cellular surveillance and persistent inflammatory activation (Wen et al., 2026; Zhou et al., 2025).

Current evidence supports a strong mechanistic relationship between mitochondrial dysfunction, mtDNA dysregulation, and cGAS-STING signaling in aging (Salminen et al., 2025). However, direct evidence connecting exercise to modulation of this pathway in the aging brain remains limited. In particular, circulating mtDNA measurements cannot by themselves establish intracellular cGAS-STING activation (Li et al., 2025). This evidence gap is important when interpreting the potential role of exercise in regulating the mitochondrial-innate immune interface.

Table 2. Representative studies linking mitochondrial dysfunction, mtDNA, and cGAS-STING signaling during aging.

Study	Experimental model	Key mitochondrial / mtDNA finding	cGAS-STING-related finding	Relevance to aging
(White et al., 2014)	Mammalian cells; mouse models	Bak/Bax-mediated mitochondrial damage promoted mtDNA release	Cytosolic mtDNA activated cGAS-STING and type I IFN production	Established mitochondrial DNA release as a potent innate immune trigger
(Rongvaux et al., 2014)	Mammalian cells; mouse models	Mitochondrial DNA released during mitochondrial outer-membrane permeabilization	mtDNA induced cGAS-dependent type I IFN responses; apoptotic caspases limited this response	Demonstrated that mitochondrial damage can be coupled to inflammatory DNA sensing
(West et al., 2015)	Cellular models of mtDNA stress	TFAM deficiency disrupted mtDNA organization and promoted mtDNA escape into the cytosol	Cytosolic mtDNA activated cGAS-STING-IRF3 signaling and interferon responses	Provided direct mechanistic evidence connecting mtDNA instability with innate immune signaling
(Tigano et al., 2021)	Mammalian cellular models	Mitochondrial DNA double-strand breaks compromised mitochondrial genome integrity and generated a retrograde immune response	Activated mitochondrial retrograde immune surveillance, with mtRNA-dependent RIG-I/MAVS signaling reported rather than a direct cGAS-STING mechanism	Demonstrates that mtDNA damage can initiate mitochondria-to-nucleus inflammatory signaling, providing mechanistic context for mitochondrial stress and innate immune activation
(Jiménez-Loygorri et al., 2024)	Young and aged mito-QC mice; human fibroblasts	Aging was associated with cytosolic mtDNA accumulation despite stable or increased mitophagy	Increased cytosolic mtDNA was associated with cGAS-STING activation and type I IFN signaling	Identified mitochondrial quality control as an important regulator of age-associated mtDNA-dependent inflammation
(Li et al., 2024)	Postmitotic muscle cells; aging models	mtDNA release increased with mitochondrial dysfunction and cellular aging	mtDNA release promoted cGAS-STING activation	Extended the mtDNA-cGAS-STING-aging relationship to postmitotic muscle tissue

Exercise, Mitochondrial Quality Control, and Brain Aging

Regular exercise can influence mitochondrial function beyond skeletal muscle and may contribute to the maintenance of brain metabolic and inflammatory homeostasis during aging (Zhou et al., 2026). Exercise promotes mitochondrial biogenesis, antioxidant capacity, and mitochondrial turnover, while repeated training can improve the ability of cells to tolerate metabolic stress (El Assar et al., 2022). These adaptations are relevant to the aging brain, where high energetic demands and progressive mitochondrial dysfunction may increase neuronal and glial vulnerability (Burtscher et al., 2021).

Mitochondrial quality control is particularly important because the efficient removal of dysfunctional mitochondria can limit the accumulation of damaged mitochondrial components

(Picca et al., 2023). Exercise associated stimulation of mitophagy and mitochondrial remodeling may therefore help maintain mitochondrial integrity and reduce persistent cellular stress (Cai et al., 2026). In contrast, age-related impairment of mitochondrial turnover may increase the likelihood that damaged mitochondria persist and contribute to mtDNA dysregulation (Wang et al., 2023).

The effects of exercise on the brain are likely to involve both local and systemic mechanisms. Changes in cerebral metabolism, vascular function, and neural activity may interact with peripheral adaptations originating from skeletal muscle (Liang et al., 2021). Exercise-induced changes in systemic metabolic and signaling environments may consequently contribute to the regulation of brain mitochondrial function and neuroimmune homeostasis (Feng et al., 2026). However, current evidence does not support a single peripheral mediator as responsible for these effects.

Microglia may represent an important cellular interface between mitochondrial homeostasis and neuroinflammation. Aging can alter microglial metabolic and inflammatory states, while mitochondrial dysfunction may further influence their response to endogenous danger signals (Mela et al., 2020). By improving mitochondrial quality control and stress resistance, regular exercise may reduce the persistence of mitochondrial signals capable of promoting inflammatory activation (Choi et al., 2024). This provides a potential upstream mechanism through which exercise could influence age-related neuroinflammation (Mee-Inta et al., 2019).

Nevertheless, the direct relationship between exercise-induced mitochondrial adaptation and brain cGAS-STING activity remains insufficiently established. Most studies have examined mitochondrial function, inflammatory markers, or neurological outcomes independently rather than measuring mitochondrial stress, mtDNA localization, and cGAS-STING signaling simultaneously (Zhu et al., 2026). Therefore, the current evidence supports a plausible mechanistic connection but does not establish that exercise directly suppresses cGAS-STING signaling in the aging brain (Ma et al., 2026).

The different levels of evidence considered in this review provide complementary support for the proposed exercise–mitochondrial adaptation–brain cGAS-STING relationship. Human and skeletal muscle studies provide evidence that exercise can promote mitochondrial remodeling, enhance mitochondrial quality-control capacity, and modulate redox homeostasis, thereby establishing a physiological basis for exercise-induced mitochondrial adaptation (El Assar et al., 2022; Zhou et al., 2026). Experimental animal studies extend these observations

to the brain, with evidence that exercise can improve mitochondrial quality control and preserve mitochondrial function and redox balance in aging-related brain regions, including the hippocampus and cortex (Luo et al., 2017; Mesquita et al., 2022; Cai et al., 2026). In parallel, cellular and animal studies provide mechanistic evidence that mitochondrial damage, mtDNA release, or cytosolic mtDNA accumulation can activate cGAS-STING signaling and promote inflammatory responses (White et al., 2014; Rongvaux et al., 2014; Tigano et al., 2021; Li et al., 2024). Taken together, these findings support a biologically plausible sequence in which exercise-induced mitochondrial adaptation may influence mtDNA homeostasis and thereby modify conditions that favor cGAS-STING activation. However, these evidence levels should not be interpreted as demonstrating a direct causal pathway from exercise to brain cGAS-STING signaling. Direct evidence simultaneously linking exercise, mitochondrial adaptation, mtDNA localization, and cGAS-STING activity in the aging human brain remains limited (Zhu et al., 2026; Ma et al., 2026). Thus, the proposed relationship represents an integrative mechanistic framework supported by convergent evidence across experimental levels rather than an established causal pathway.

Overall, exercise appears to promote conditions that favor mitochondrial maintenance and stress resolution. These adaptations may limit sustained mitochondrial dysfunction and consequently reduce the cellular conditions that favor mtDNA-dependent inflammatory signaling. This relationship provides the basis for considering exercise dose and biological resilience as potential determinants of whether mitochondrial stress remains adaptive during aging (Feng et al., 2026; Zhou et al., 2026).

Exercise Dose, Aging, and the Mitochondrial Stress-Resolution Threshold

The adaptive effects of exercise depend on the relationship between exercise-induced mitochondrial stress and the capacity of tissues to resolve that stress (Botella et al., 2025). Exercise intensity, duration, frequency, training status, and recovery can influence the magnitude and persistence of mitochondrial perturbation (Mølmen et al., 2025). Thus, increasing exercise exposure does not necessarily produce proportionally greater mitochondrial benefit (Cardinale et al., 2021). An appropriately dosed exercise stimulus can generate transient metabolic and redox stress that activates mitochondrial biogenesis, antioxidant responses, and quality-control mechanisms (Turkel et al., 2025). With adequate recovery, repeated exposure may increase mitochondrial capacity and improve resistance to subsequent stress (Taskin et al., 2022). In contrast, excessive or insufficiently recovered exercise may prolong mitochondrial perturbation and reduce the efficiency of cellular

recovery (Özdemir & Demir, 2025). This distinction supports the concept of a mitochondrial stress-resolution threshold, in which the biological outcome depends on whether exercise-induced stress remains within the capacity of mitochondrial quality-control systems (Gorgori-Gonzalez et al., 2026). Aging may shift this threshold by reducing mitochondrial turnover, mitophagy, antioxidant capacity, and mtDNA maintenance (Yun et al., 2026). Consequently, an exercise stimulus that is readily resolved in a metabolically resilient individual may produce a more persistent mitochondrial response in an older or metabolically compromised individual (Abrego-Guandique et al., 2025). Importantly, this concept does not imply that exercise becomes detrimental with age; rather, it suggests that exercise dose should be considered in relation to biological resilience and recovery capacity.

This framework may also explain variability among exercise studies (Lim et al., 2022). Individuals performing the same externally prescribed exercise may experience different intracellular mitochondrial stresses because of differences in age, fitness, metabolic health, training history, and recovery (Mølmen et al., 2025; Özdemir & Demir, 2025). External workload may therefore not accurately represent the biological dose experienced by mitochondria. Taken together, these relationships support a model in which the biological effect of exercise depends on whether exercise-induced mitochondrial stress remains within the individual's capacity for effective stress resolution, as illustrated in Figure 1.

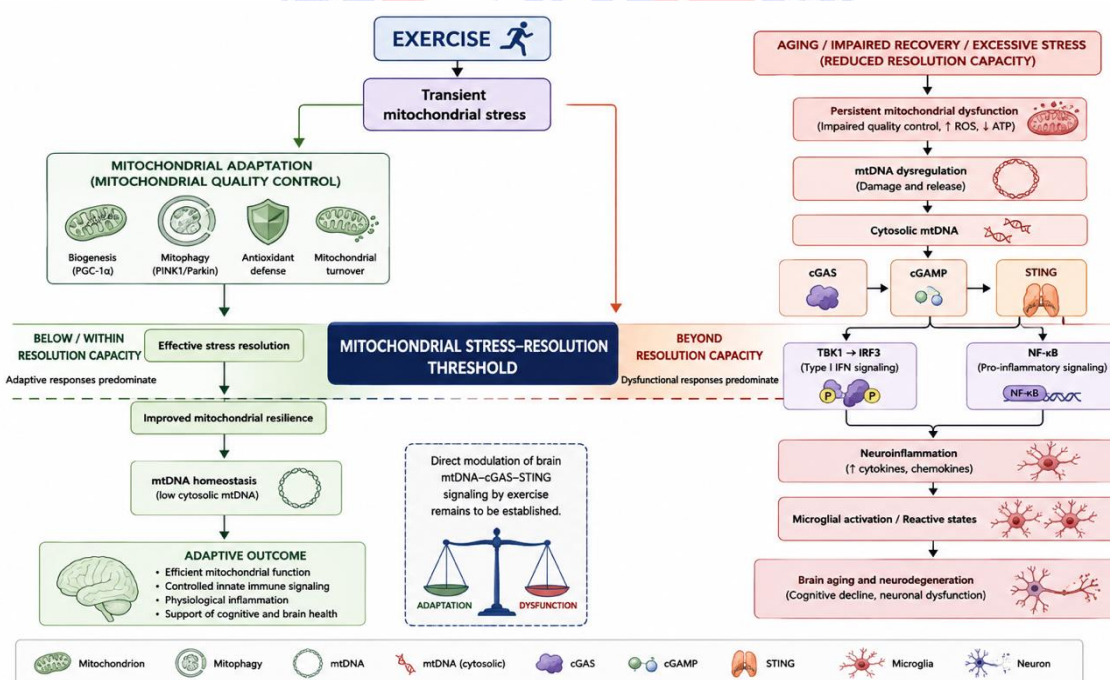


Figure 1. Proposed exercise-mitochondria-mtDNA-cGAS-STING framework in healthy brain aging.

At present, however, this model remains hypothesis-generating. Few studies have simultaneously examined exercise dose, mitochondrial quality control, cytosolic mtDNA, and cGAS-STING signaling, particularly in aged human populations. Future studies should therefore determine whether markers of mitochondrial stress and recovery can predict individual responses to exercise and whether these responses are associated with changes in cGAS-STING activity and neurological function (Mănescu et al., 2026).

DISCUSSION and CONCLUSION

The evidence reviewed in this article supports a potential mechanistic relationship between exercise-induced mitochondrial adaptation, mtDNA homeostasis, cGAS-STING signaling, and brain aging. Exercise imposes a transient mitochondrial challenge that can stimulate adaptive responses, whereas aging is associated with reduced mitochondrial quality control and increased susceptibility to persistent cellular stress. The interaction between these processes may determine whether mitochondrial stress is resolved through adaptation or persists sufficiently to contribute to inflammatory signaling.

A key implication is that exercise should not be viewed simply as an anti-inflammatory intervention. Its physiological effects may instead arise from repeated cycles of controlled stress and recovery that improve mitochondrial resilience. Enhanced mitochondrial quality control may reduce the persistence of damaged mitochondria and limit the availability of mtDNA-associated danger signals. In this context, cGAS-STING may represent a downstream pathway influenced by mitochondrial homeostasis rather than a direct molecular target of exercise.

The proposed mitochondrial stress-resolution threshold provides a framework for interpreting this relationship. Appropriate exercise exposure may promote mitochondrial remodeling and increase stress tolerance, whereas excessive stress or inadequate recovery may exceed the capacity of mitochondrial quality-control systems. Aging may further modify this balance by reducing mitochondrial turnover and recovery capacity. This model may therefore help explain why exercise responses vary according to age, fitness, metabolic status, training history, and recovery.

The evidence connecting mtDNA-cGAS-STING signaling with aging and neuroinflammation is stronger than the evidence directly linking exercise to this pathway. Experimental studies support a role for mitochondrial dysfunction and cytosolic DNA in cGAS-STING activation and age-related inflammatory responses, particularly in microglia.

However, direct studies demonstrating that exercise alters brain cGAS-STING activity through changes in mtDNA homeostasis remain limited. Therefore, the exercise-mitochondria-cGAS-STING relationship should currently be considered a plausible and testable mechanistic framework rather than an established causal pathway.

Future studies should simultaneously assess exercise exposure, mitochondrial quality control, mtDNA localization, and cGAS-STING activity. Such approaches would help determine whether improvements in mitochondrial stress resolution are associated with reduced persistent innate immune activation and better neurological outcomes during aging. Individual differences in age, sex, fitness, metabolic health, and recovery should also be considered when evaluating the biological effects of exercise.

Overall, exercise may contribute to healthy brain aging not by eliminating mitochondrial stress or suppressing innate immune signaling, but by improving the capacity to tolerate and resolve physiological stress. The mitochondrial stress-resolution threshold proposed here provides a concise framework connecting exercise physiology with mitochondrial quality control, mtDNA-dependent immune signaling, and neuroinflammation. Validation of this framework could provide a mechanistic basis for more individualized exercise strategies aimed at preserving brain health and healthspan.

Suggestions

Future research should directly investigate the relationship between exercise dose, mitochondrial stress, mtDNA homeostasis, and cGAS-STING signaling during aging. Experimental studies should distinguish acute exercise responses from long-term training adaptations and include adequate recovery periods. Simultaneous assessment of mitochondrial quality-control markers, cytosolic mtDNA, cGAS-STING activation, and inflammatory responses would provide stronger mechanistic evidence than isolated measurement of circulating mtDNA or inflammatory cytokines.

Longitudinal studies in older adults are particularly needed to determine whether improvements in mitochondrial stress-resolution capacity are associated with changes in neuroinflammatory signaling and cognitive or functional outcomes. Exercise intensity, modality, training status, sex, metabolic health, and recovery should be considered when evaluating individual responses. Identifying biomarkers of mitochondrial stress and recovery may ultimately support more individualized exercise prescriptions for healthy aging.

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