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Review Article

Molecular Crosstalk at the Mitochondrial Stress-Immunity Interface: Melatonin's Role in Mitochondrial DNA Sensing, cGAS-STING Signaling, and the Mitochondrial Integrated Stress Response: A Review

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Abstract

This review addresses the molecular interplay at the interface between mitochondrial stress and innate immunity, focusing on the role of melatonin in regulating mtDNA release, its sensing pathways via cGAS-STING, and the integrated mitochondrial stress response (ISR). The literature shows that mitochondrial stress resulting from hypoxia, ionizing radiation, lysosomal dysfunction, or toxins and therapeutics may lead to leakage of mtDNA into the cytosol, where it is sensed via cGAS-STING and stimulates the production of type I interferons and inflammatory cytokines. These pathways interact with the ISR, which resets nuclear gene expression, limits consumptive metabolic processes, and promotes autophagy and mitochondrial protein homeostasis. Melatonin is emerging as a multifaceted modulatory factor: it maintains mitochondrial fitness, reduces mtDNA leakage, modulates the intensity of STING activation in context-dependent ways, and regulates the ISR-associated transcriptional program. Evidence suggests that these effects are manifested in disease contexts including inflammation, aging, neurodegeneration, and metabolic disorders. The review concludes that the mtDNA-cGAS-STING–ISR axis represents a promising therapeutic target, and that melatonin may be an integrative intervention to restore immune-metabolic homeostasis upon mitochondrial stress, with further studies needed to precisely determine its regulatory mechanisms.

Keywords: Melatonin; Mitochondrial DNA; cGAS–STING Pathway; Integrated Stress Response; Innate Immunity.

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1. Introduction

Mitochondria serve as metabolic hubs that orchestrate a range of bioenergetic and biosynthetic processes essential for sustaining cellular homeostasis (1). Environmental and intentional perturbations can lead to mitochondrial stress, affecting ATP generation and promoting the release of mitochondrial damage-associated molecular patterns (DAMPs), including mitochondrial DNA (mtDNA) (2). The liberation of mtDNA from the organelle into the cytosol activates innate immune responses that are sensed by the cyclic GMP-AMP (cGAMP) synthase (cGAS) stimulator of interferon genes (STING) pathway (3). Moreover, mitochondrial stress engages the mitochondrial integrated stress response (ISR) that inhibits nutrient-consuming anabolic processes, curtails growth, fosters autophagy, and augments mitochondrial proteostasis. ISR activation further modulates immune gene expression and regulates pro-inflammatory and anti-viral host defenses (4).

Emerging evidence indicates that mtDNA release, cGAS-STING signaling, and the ISR form an

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interconnected network through which signals propagate in positive or negative directions (5). The cGAS-STING pathway represents a central conduit for the perception of cytosolic mtDNA, whereas the mitochondrial ISR can be engaged concomitantly with cGAS-STING activation (6). Physiological or pathological states that promote mitochondrial stress may thus serve as initiating events capable of triggering immune-modulatory circuits governed by the cGAS-STING pathway and the ISR (7). Melatonin acts as an agent that modulates the mtDNA sensing cGAS–STING signaling–ISR interface. The indoleamine upholds mitochondrial fitness under stress, thereby mitigating the extent of mtDNA leakage and the amplitude of cGAS–STING output (4). When cGAS-STING signaling is initiated, melatonin exerts additional influence to reshape the output of the pathway. In parallel, the mitochondrial ISR is also engaged, and melatonin serves to fine tune the transcriptional program elicited by this circuit (2).

2. Background on Mitochondrial Stress and Innate Immunity

Mitochondria play essential roles in energy metabolism and innate immunity. They can release signals (i.e., damage-associated molecular patterns, DAMPs) that activate pattern recognition receptors (PRRs) to regulate proinflammatory responses. Mitochondrial stress also induces the release of mitochondrial DNA (mtDNA), which serves as an endogenous DAMP that circulates within organisms and acts as an immune modulator (8). Four main types of mitochondrial stress lead to mtDNA release: (1) hypoxia (when mitochondrial respiration is impaired and adenosine triphosphate concentrations drop, overproducing reactive oxygen species), (2) ionizing radiation (when mitochondria are damaged and the permeability transition pore opens), (3) lysosome dysfunction (as occurs in lysosomal storage disorders), and (4) exposure to chemotherapeutics or neurodegenerative agents (6). Released mtDNA activates the cytosolic cGAS-STING axis, which induces type I interferon (IFN-I) signaling and inflammation (5). In turn, IFN-I can dampen further mtDNA release, suggesting a potential negative-feedback mechanism involving the cGAS-STING pathway from the nucleus, upstream of the mitochondrial integrated stress response (ISR) and crucial for mitochondrial resilience (4).

Different forms of stress, but not all, trigger mtDNA release; the pathways, receptors, and downstream responses associated with mtDNA vary across stress types; and crosstalk is evident among cGAS and other cytosolic PRRs that detect mtDNA (4). Note Figure 1.

3. Melatonin: Biosynthesis, Functions, and Immunometabolic Roles

Melatonin is a ubiquitous indoleamine, synthesized in vertebrates from tryptophan in a series of reactions that include serotonin as an intermediate (9). Melatonin is deeply involved in a group of physiological functions regulating the vitally important steady state of cells, organs, tissues, and organisms. Circadian rhythms, seasonal stimuli, reproduction, regulation of skin color, mediating the effects of sunlight, sleep-wake cycles, maintenance of free radical generation and removal, regulation of neuronal and mental states, control of energy metabolism, cooperation with the neurohormonal system, and multifarious biological motions all reflect physiologically active melatonin (4). Fundamental roles in immunity, cell death, and mitochondrial homeostasis are increasing awareness of the importance of melatonin in immunometabolism (10). Melatonin modulates stressors eliciting diverse immunogenic signals by regulating mtDNA release, cGAS-STING signaling initiation, and mitochondria-integrated stress pathways (4). Note Figure 2.

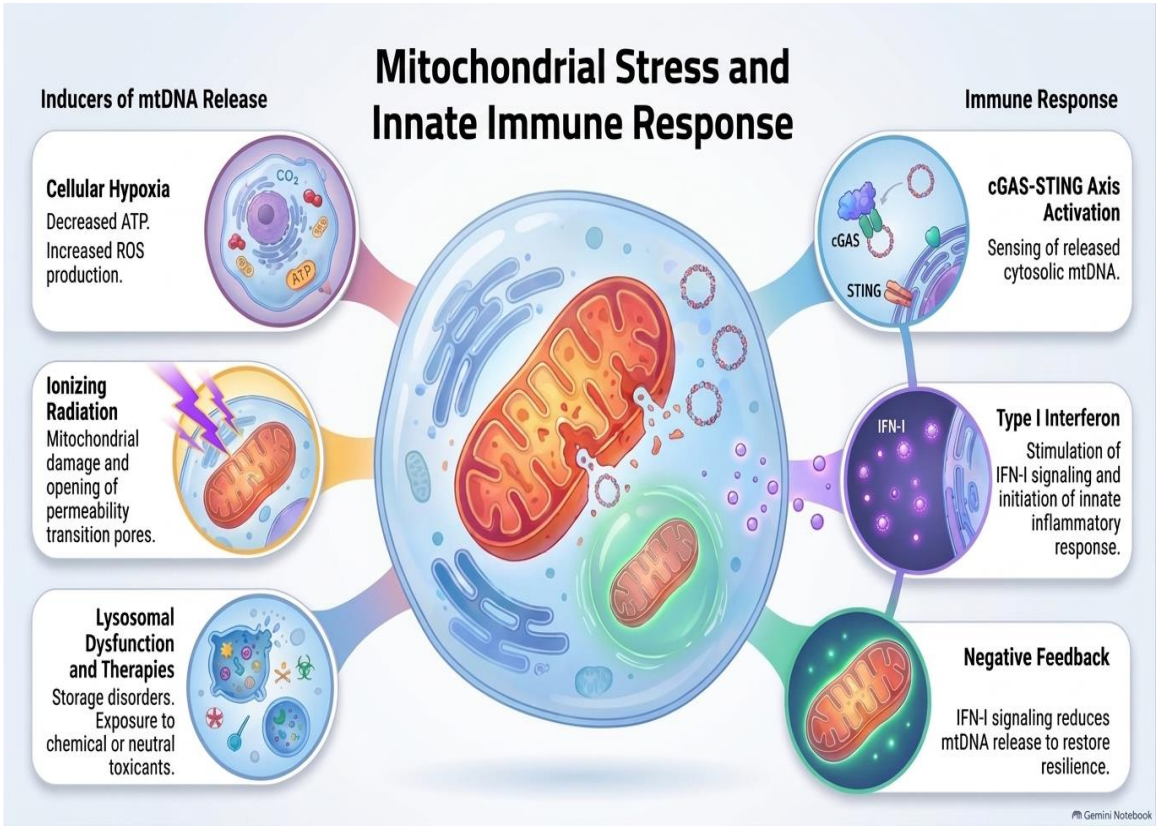


Figure (1): Mitochondrial Stress and Innate Immunity (designed using Gemini Notebook)

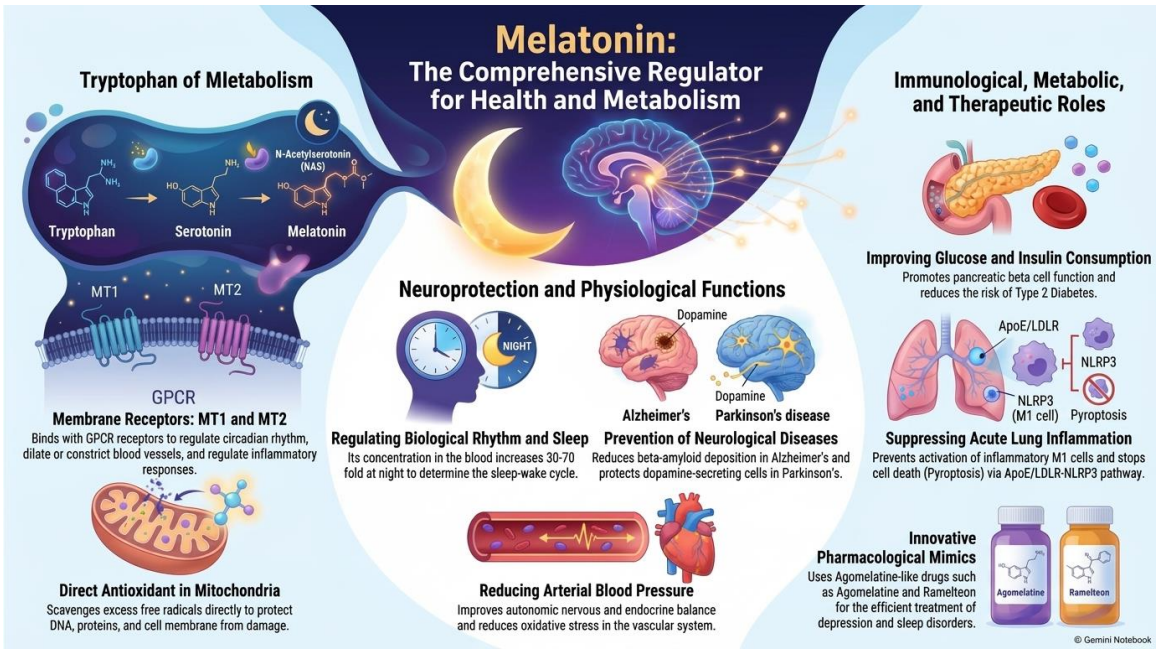


Figure 2: Immune metabolism and melatonin biological functions (designed using Gemini Notebook)

4. mtDNA Sensing and the cGAS-STING Pathway: Mechanisms and Regulation

Mitochondrial DNA (mtDNA) is released in various forms from organelles or as extracellular vesicles during cellular stress (11). cGAS recognizes mtDNA and produces cyclic GMP-AMP (cGAMP), activating the STING signaling pathway (6). STING stimulation recruits TANK-binding kinase 1 (TBK1) and induces the phosphorylation of interferon regulatory factor 3 (IRF3), promoting the expression of type I interferons (IFNs) and proinflammatory cytokines. In parallel, STING activation upregulates NF-κB-target genes, which are involved in proinflammatory processes. Thus, cGAS-STING signaling provides an interface for mitochondrial stress to mediate immune responses (12).

Both nucleic acid topology and release mechanisms define mtDNA as a pathogen-associated molecular pattern (PAMP) or danger-associated molecular pattern (DAMP) that activates the cGAS-STING pathway (12). Oligomerization of cGAS and formation of cGAMP occur more readily upon exposure to cytosolic mtDNA compared to extracellular mtDNA. Melatonin enhances interactions between cGAS and DNA, prolongs cGAMP production, and maintains intracellular rather than secreted mtDNA forms (13). Mitochondrial and broader cellular energy production are likewise promoted by melatonin, which sustains the cGAMP signal, underscoring the multifaceted role of this metabolite in modulating the mitochondrial stress–immunity interface (12,13). Note Figure 3.

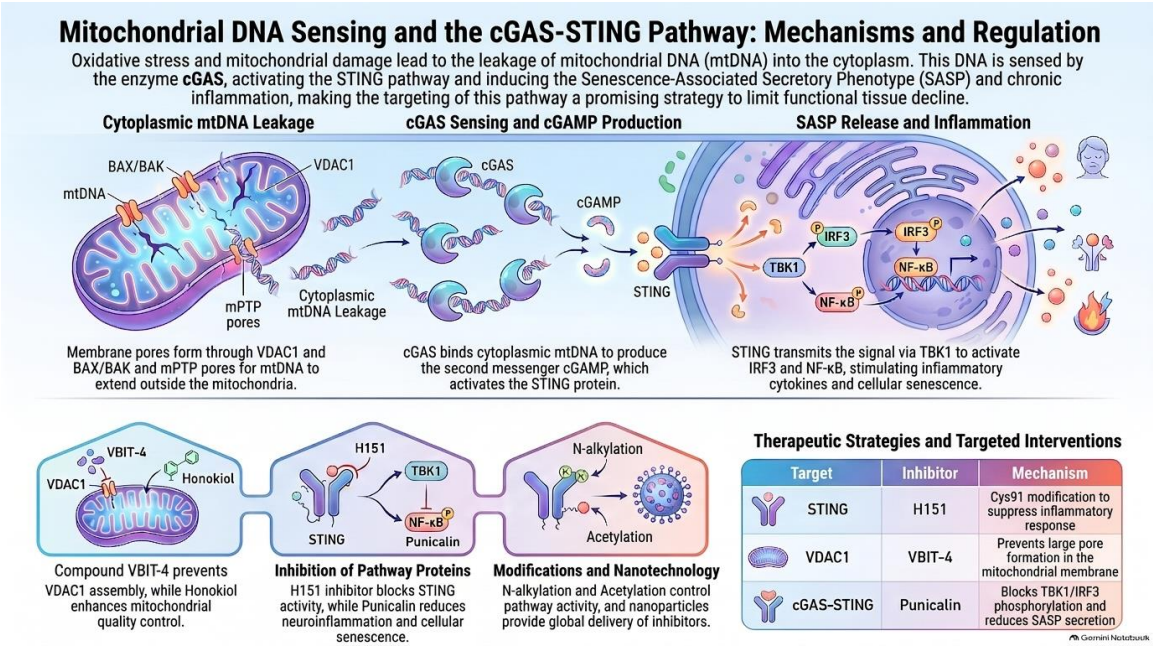


Figure 3: Mechanisms and regulation of mtDNA sensing and the cGAS–STING pathway (designed using Gemini Notebook)

5. The Mitochondrial Integrated Stress Response and Its Immunological Implications

Mitochondria play a pivotal role in cellular energy production and metabolism. Given that mitochondria serve as vital cellular organelles, they are relevant not only for energy generation but also for intracellular signaling, metabolic homeostasis, and cell cycle regulation (14). These pivotal functions suggest that disturbances of mitochondrial homeostasis can negatively impact cellular physiology, resulting in the emergence of pathological conditions. Recently, considerable interest has been directed to the concept that mitochondrial dysfunction combined with other stressors may lead to metabolic alterations that serve as signals for immune activation (5,9). Aspects of mitochondrial dysfunction can generate pro-inflammatory signals, thereby underscoring significant crosstalk between metabolic homeostasis, mitochondrial physiology, and the innate immune system (5).

Mitochondria have also been proposed to function as a cytosolic surveillance system, coordinating metabolism and immunity by monitoring the cytosolic accumulation of metabolic intermediates (8). Intriguingly, bioenergetic stress triggered by the inhibition of mitochondrial respiration has been linked to the induction of antimicrobial genes in a pattern-recognition-receptor-independent manner (15). Mitochondrial dysfunction in specific cell types can be sensed by the cytosolic pattern-recognition receptors cGAMP synthase (cGAS) and absent in melanoma 2 (AIM2), which, respectively, recognize mitochondrial DNA (mtDNA) and mtRNA (6). These pathways are coordinated by the mitochondrial integrated stress response (ISR), which adjusts nuclear gene expression in response to mitochondrial perturbation, highlighting the crosstalk that exists between metabolism, immunity, and mitochondrial physiology (16).

6. Crosstalk Between mtDNA Sensing, cGAS–STING Signaling, and the Mitochondrial ISR

Mitochondrial stress triggers key immune signalling pathways through mtDNA release, highlighting a stress immunity interface that coordinates cellular responses to mitochondrial dysfunction. Damaged mtDNA activates the cGAS-STING pathway, resulting in a type I interferon transcriptional programme and the induction of pro-inflammatory cytokines (5,6). Recent studies have also established links between cGAS-STING signalling and the mitochondrial integrated stress response (ISR). Mitochondrial perturbations promote the synthesis of mitochondrial single-stranded RNA and inducible cAMP early repressor (ICER), both of which dampen cGAS activity and restrict STING activation (15). Those mechanisms limit overactive type I interferon responses during the early phase of mitochondrial stress and facilitate the transition to an ISR-mediated phase (11). The same mitochondrial stressors that provoke cGAS-STING signalling also elicit the ISR, underscoring an important aspect of mitochondrial stress–immunity crosstalk (17). Note Figure 4.

7. Melatonin at the Interface: Modulation of mtDNA Sensing and STING Activation

Melatonin has been considered a modulatory factor at the mitochondrial stress-innate immunity interface. Several recent findings indicate that melatonin participates in event sequences pivotal for efficient immunometabolic adaptation to mitochondrial insults, especially mtDNA sensing through the cGAS-STING pathway and the mitochondrial integrated stress response (ISR). Despite this emerging role, the mode of action of melatonin during these processes remains only partially defined (17,18).

On the cGAS-STING signaling side, melatonin inhibits mtDNA release during metabolic disorders and bacterial infections, reduces STING activation, and improves mitochondrial function; relief from mitochondrial dysfunction appears to mediate the

last two effects (19). Conversely, the evidence supports an enhancing role for melatonin in STING activation in other settings: during SARS-CoV-2 infection, in NK and T-cell effector functions, and during mtDNA sensing triggered by Haemophilus parasuis (7). Context-dependent modulation of STING activation during infection by multihit pathogens is consistent with alignments between the cGAS-STING pathway and the mitochondrial ISR, which couples the detection of mtDNA signals to an appropriate immunometabolic response. Altogether, the available evidence indicates that melatonin must engage appropriately with this crossroad for efficient immunometabolic adaptation (4).

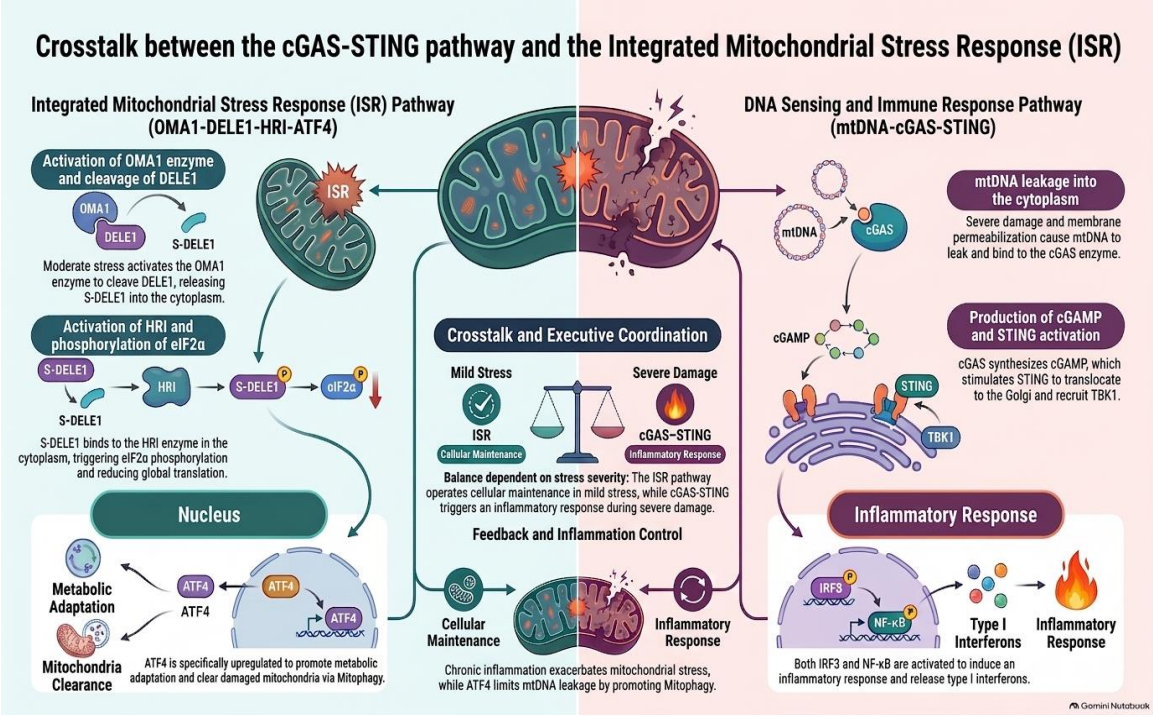


Figure 4: Mitochondrial stress signaling and inflammation (designed using Gemini Notebook)

8. Evidence Linking Melatonin to Mitochondrial Stress Responses and Immune Outcomes

Numerous in vitro and in vivo studies establish a clear linkage between melatonin and effects on mitochondrial stress pathways, correlated with a broad spectrum of metabolic and immunological outcomes (20). The specific operational context, timing, duration, concentration, and particular model systems employed, however, exert a decisive influence on the observed responses. Early studies often focused on the circadian synchronization and antioxidant roles of melatonin. More recent experimental paradigms reveal broad involvement of this molecule in what can be termed an "immunometabolomics" framework, where immune and metabolic pathways exert bidirectional regulatory control over one another (17).

For example, melatonin prevents the proinflammatory programmed release of mtDNA following lipopolysaccharide stimulation in macrophages yet downregulates the antimitochondrial response to the chronic, low-grade inflammation characteristic of aging and obesity (15). In these studies, the immunoregulatory

action invariably arises from doses in the nanomolar range and relatively brief exposure intervals, which sufficiently economize cellular resources to enable reestablishment of normal circadian or metabolic scheduling. In contrast, the extensive cytoplasmic accumulation of mtDNA that accompanies crippling mitochondrial impairment and impedes normal energetic recovery in states of metabolic disorder proceeds in concert with a concomitant rise in endogenous melatonin levels (4). This interplay emphasizes the duality of melatonin as both an immunoregulatory signal and a marker of cellular distress, illuminating its pivotal role at the mitochondrial stress immunity interface (15).

Other instances involve direct feedback-linked influence on cellular metabolic controls and nutriform exchange. Interference with trembler protein1 or lipid transport regulates the release of extracellular vesicles, which mediate intercellular exchanges of metabolites and secondary messengers (19). Such material exchange has further emerged as an important mechanism for coordinating control of mitochondrial metabolism and distribution of immunoregulatory activities, temporal delimitation, synergetic combination with alternate hormonal signals, and variation in nutrient availability from the microenvironment, which remain key regulatory factors shaping the modulation of stress immunity crosstalk (21).

9. Pathophysiological Contexts: Inflammation, Aging, Neurodegeneration, and Metabolic Disease

Melatonin's modulatory effects at the mitochondrial stress immunity interface emerge through cellular contexts associated with harmful inflammation, aging, neurodegeneration, and metabolic dysregulation. Across many inflammatory disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and diabetes mellitus, melatonin supplementation alleviates disease manifestations in animal models (22). Consistently, anti-inflammatory outcomes follow melatonin administration in murine models of experimental autoimmune encephalomyelitis, a model of multiple sclerosis, and in transgenic mouse models of Alzheimer's disease. Under conditions mimicking systemic aging, the extent of melatonin's protective effects declines with advanced chronological age in rodents, and the loss of an age-associated increase in brain melatonin parallels cognitive decline and neuroinflammation. The substantial dosage requirement for the transcriptional and immunological outcomes of melatonin treatment, including the modulation of cGAS-STING-TBK1 signaling and the expression of pro-inflammatory cytokines, suggests restricted availability or heightened inactivation of the indoleamine in aging neurons. These observations are consistent with key characteristics of the mitochondrial ISR and its crosstalk beyond metabolism (7,9).

In metabolic syndrome, characterized by the co-occurrence of obesity, insulin resistance, dyslipidemia, and hypertension, melatonin restores metabolic abnormalities in preclinical models of high-fat-diet-induced obesity. Treatment of rodents with high-induction histone-acetylation drugs, which spoil silencing of the pro-opiomelanocortin (POMC) gene and stimulate synthesis of the autonomic-balance-restoring α-melanocyte-stimulating-hormone (α-MSH), also improves metabolic dysregulation and extends lifespan. Melatonin can reactivate the dormant POMC gene in aged POMC-silenced mice that had been on a standard diet without histone-acetylation-promoting drugs, representing a protective and longevity-enhancing action specific to the aging phenotype. In addition, melatonin signals this prevention of metabolic syndrome and life extension through TRPA1-mitochondria-cAMP circuits that temporally and spatially boost mitochondrial energy bioavailability (5,19). These findings suggest that both the circulatory delivery of excess melatonin, capable of stimulating transcriptional and immunological outputs across tissues, and its

feedback-mediated mitochondrial-targeted action at the early phase circadian increasing stability period of mitochondria cycle remain viable strategies for further studies aimed at characterizing the cross-regulation of mitochondrial immunity stresses intimately linked to increased pro-ageing inflammatory burdens (23).

10. Therapeutic Implications and Future Directions

A systems biology perspective suggests that targeting mitochondrial physiology represents an attractive immunomodulatory approach for diseases associated with climate change, such as neurodegeneration (5). Nonetheless, the cGAS-STING pathway remains a legitimate target, as it has been implicated in immunometabolic dysregulation and inflammatory processes (24). Downstream, cGAS, nuclear factor-κB (NF-κB) and interferon regulatory factor 3 (IRF3) govern proinflammatory cytokines and type I interferon (IFN) synthesis. These signals regulate the transcription of mitochondrial stress response factors (25), providing a template for future studies to establish whether modulation of the cGAS–STING pathway could enhance the immune benefits of other MitoS (23).

Consideration of mitochondrial stress immunity crosstalk highlights the attractiveness of melatonin as an integrative therapeutic, as it has the potential to restore homeostasis when no single intervention suffices. Melatonin acts via multiple mitochondrial immune nodes, addressing distinct stressors originating from the same organelle. In addition to preventing mtDNA leakage, melatonin counters mitochondrial permeability transition pore (mPTP)-mediated collapse of mitochondrial membrane potential (ΔΨm), restoring proteostasis, redox equilibrium, and bioenergetics, which improve the synthesis and release of energetically costly proinflammatory mediators. Furthermore, melatonin–cGAS-STING connections extend beyond mtDNA leakage, as it promotes the mitochondrial integrated stress response (ISR) even when cGAS remains suppressed. Under these conditions, indirect cGAMP synthesis may still stimulate STING, linking cGAS to the mitochondrial ISR and opening further avenues for therapeutic exploration (5,14).

11. Conclusion

This review suggests that mitochondrial stress releases mtDNA into the cytosol, where it is sensed via the cGAS-STING pathway and stimulates type I IFNs and inflammatory cytokines, intersecting with the mitochondrial integrase stress response (ISR) that resets nuclear expression and promotes autophagy and protein homeostasis. Melatonin emerges as a multifaceted modulatory agent; It maintains mitochondrial fitness, reduces mtDNA leakage, modulates the intensity of STING activation in context-dependent ways, and regulates the ISR-associated transcriptional program. These effects are manifested in inflammation, aging, neurodegeneration, and metabolic disorders. Therefore, the mtDNA-cGAS-STING-ISR axis represents a promising therapeutic target, and melatonin may be an integrative intervention to restore immune-metabolic homeostasis, with additional studies needed to precisely clarify its regulatory mechanisms.

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References:

1- Shen, K., Pender, C. L., Bar-Ziv, R., Zhang, H., Wickham, K., Willey, E., ... & Dillin, A. (2022). Mitochondria as cellular and organismal signaling hubs. Annual review of cell and developmental biology, 38(1), 179-218.

2- Zanini, G., Selleri, V., Lopez Domenech, S., Malerba, M., Nasi, M., Mattioli, A. V., & Pinti, M. (2023). Mitochondrial DNA as inflammatory DAMP: a warning of an aging immune system? Biochemical Society Transactions, 51(2), 735-745.

3- Aloraini, G. S. (2025). Mitochondrial DNA release and cGAS-STING activation: Emerging insights into anti-tumor immunity. *Pathology-Research and Practice*, 156158.

4- Bilen, M., Benhammouda, S., Slack, R. S., & Germain, M. (2022). The integrated stress response as a key pathway downstream of mitochondrial dysfunction. Current Opinion in Physiology, 27, 100555.

5- Tao, G., Liao, W., Hou, J., Jiang, X., Deng, X., Chen, G., & Ding, C. (2024). Advances in crosstalk among innate immune pathways activated by mitochondrial DNA. *Heliyon*, *10*(1).

6- Liu, J., Zhou, J., Luan, Y., Li, X., Meng, X., Liao, W., ... & Wang, Z. (2024). cGAS-STING, inflammasomes and pyroptosis: an overview of crosstalk mechanism of activation and regulation. *Cell Communication and Signaling*, *22*(1), 22.

7- Zhang, H., Li, X., Fan, W., Pandovski, S., Tian, Y., & Dillin, A. (2023). Inter-tissue communication of mitochondrial stress and metabolic health. *Life metabolism*, *2*(1), load001.

8- Luna-Sánchez, M., Bianchi, P., & Quintana, A. (2021). Mitochondria-induced immune response as a trigger for neurodegeneration: a pathogen from within. *International journal of molecular sciences*, *22*(16), 8523.

9- Reiter, R. J., Tan, D. X., Rosales-Corral, S., Galano, A., Jou, M. J., & Acuna-Castroviejo, D. (2018). Melatonin mitigates mitochondrial meltdown: interactions with SIRT3. *International journal of molecular sciences*, *19*(8), 2439.

10- Carrillo-Vico, A., Lardone, P. J., Álvarez-Sánchez, N., Rodríguez-Rodríguez, A., & Guerrero, J. M. (2013). Melatonin: buffering the immune system. *International journal of molecular sciences*, *14*(4), 8638-8683.

11- Kim, J., Kim, H. S., & Chung, J. H. (2023). Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. *Experimental & Molecular Medicine*, *55*(3), 510-519.

12- Dai, X., Hu, Y., Jiang, L., Lei, L., Fu, C., Wu, S., ... & Zeng, Q. (2023). Decreased oxidative stress response and oxidant detoxification of skin during aging. Mechanisms of ageing and development, 216, 111878.

13- Liao, G., Wang, W., Yu, J., Li, J., Yan, Y., Liu, H., ... & Fan, L. (2024). Integrated analysis of intestinal microbiota and transcriptome reveals that a coordinated interaction of the endocrine, immune system, and gut microbiota response to heat stress in Litopenaeus vannamei. Developmental & Comparative Immunology, 156, 105176.

14- Formentini, L., Santacatterina, F., de Arenas, C. N., Stamatakis, K., López-Martínez, D., Logan, A., ... & Cuezva, J. M. (2017). Mitochondrial ROS production protects the intestine from inflammation through functional M2 macrophage polarization. *Cell Reports*, *19*(6), 1202-1213.

15- Xia, Y., Zhang, Q., Ye, Y., Wu, X., He, F., Peng, Y., ... & Ren, W. (2022). Melatonergic signalling instructs transcriptional inhibition of IFNGR2 to lessen interleukin-1β-dependent inflammation. *Clinical and Translational Medicine*, *12*(2), e716.

16- Heo, J., Park, Y. J., Kim, Y., Lee, H. S., Kim, J., Kwon, S. H., ... & Cho, H. (2023). Mitochondrial E3 ligase MARCH 5 is a safeguard against DNA-PKcs-mediated immune signaling in mitochondria-damaged cells. *Cell death & disease*, *14*(12), 788.

17- Zhou, L., Zhang, Y. F., Yang, F. H., Mao, H. Q., Chen, Z., & Zhang, L. (2021). Mitochondrial DNA leakage induces odontoblast inflammation via the cGAS-STING pathway. *Cell Communication and Signaling*, *19*(1), 58.

18- Herst, P. M., Rowe, M. R., Carson, G. M., & Berridge, M. V. (2017). Functional

mitochondria in health and disease. *Frontiers in Endocrinology*, *8*, 296.

19- Luchetti, F., Carloni, S., Nasoni, M. G., Reiter, R. J., & Balduini, W. (2022). Tunneling nanotubes and mesenchymal stem cells: New insights into the role of melatonin in neuronal recovery. *Journal of Pineal Research*, *73*(1), e12800.

20- Hardeland, R. (2019). Aging, melatonin, and the pro-and anti-inflammatory networks. *International journal of molecular sciences*, *20*(5), 1223.

21- Tjahjono, E., Kirienko, D. R., & Kirienko, N. V. (2022). The emergent role of mitochondrial surveillance in cellular health. *Aging Cell*, *21*(11), e13710.

22- Chatterjee, D., Das, P., & Chakrabarti, O. (2022). Mitochondrial epigenetics regulating inflammation in cancer and aging. *Frontiers in cell and developmental biology*, *10*, 929708.

23- Sancho, D., Enamorado, M., & Garaude, J. (2017). Innate immune function of mitochondrial metabolism. *Frontiers in Immunology*, *8*, 527.

24- Chowdhury, A., Witte, S., & Aich, A. (2022). Role of mitochondrial nucleic acid sensing pathways in health and pathophysiology. *Frontiers in Cell and Developmental Biology*, *10*, 796066.

25- Conte, M., Martucci, M., Chiariello, A., Franceschi, C., & Salvioli, S. (2020, October). Mitochondria, immunosenescence and inflammaging: a role for mitokines?. In *Seminars in Immunopathology* (Vol. 42, No. 5, pp. 607-617). Berlin/Heidelberg: Springer Berlin Heidelberg.