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Melatonin and Human Mitochondria: Physiology, Pathochemistry, and Immunogenetics

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Abstract: ***Melatonin is traditionally viewed as a nocturnal chronobiotic secreted by the pineal gland; however, its modern biology is inseparable from mitochondria. A substantial body of evidence indicates that melatonin accumulates within mitochondria, may also be synthesized within mitochondria., and protects bioenergetics by restraining oxidative injury, stabilizing electron transport, and modulating permeability transition and intrinsic apoptosis. Beyond these well-established redox functions, melatonin influences mitochondrial network behavior (fusion–fission balance), mitophagy, and transcriptional programs governing antioxidant defenses and inflammatory tone. These functions are increasingly relevant to human pathochemistry, including neurodegeneration, cardiometabolic disease, cancer metabolism, and post-viral syndromes that converge on mitochondrial dysfunction. Finally, inter-individual variation in melatonin signaling—particularly polymorphisms in MTNR1A (MT1) and MTNR1B (MT2), and mtDNA background—supports a precision-medicine perspective in which genotype, circadian phenotype, and clinical context guide melatonin timing and dose. Here, we synthesize these mechanisms with emphasis on the Reiter school of mitochondrial melatonin biology and on Tavartkiladze's clinical and translational contributions, while retaining a structured immunogenetic framework for future trials.***

Keywords: melatonin; mitochondria; oxidative stress; MTNR1B; precision medicine

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) was first positioned in physiology as a hormonal signal of darkness and as a regulator of circadian and seasonal timing. In the last two decades, the field has converged on a deeper interpretation: melatonin is also a mitochondria-centered cytoprotective molecule whose antioxidant, anti-inflammatory, and antiapoptotic actions are unusually well matched to the vulnerabilities of oxidative phosphorylation. Reiter and colleagues framed this view by describing melatonin as a mitochondria-targeted antioxidant and, memorably, as "one of evolution's best ideas" [1].

The mitochondrial emphasis is literal and mechanistically grounded. First, mitochondria are a major source of reactive oxygen and nitrogen species (ROS/RNS) generated by the electron transport chain (ETC), especially under conditions of membrane potential instability, substrate overload, or impaired complex activity. Second, mitochondria act as decision-making organelles in cell fate through cytochrome c release, caspase activation, and permeability transition. Third, a provocative but increasingly supported concept holds that mitochondria can produce melatonin locally, implying that melatonin's primordial function may have been mitochondrial defense long before the appearance of a pineal gland. This evolutionary hypothesis was articulated for mitochondria (and chloroplasts) as ancestral sites of melatonin synthesis [2], and later strengthened by experimental evidence that mitochondria can both produce melatonin and use it to drive signaling that blocks cytochrome c release [3].

From a clinical standpoint, mitochondrial melatonin biology provides a unifying language for diverse pathologies. Neurodegenerative diseases, cardiometabolic disorders, cancer progression, and post-infectious syndromes share a common theme: sustained oxidative stress, dysregulated inflammation, and maladaptive metabolic remodeling. In this setting, melatonin's ability to stabilize mitochondria—by improving bioenergetics, constraining oxidant production, and tuning inflammatory signaling—makes it an unusually versatile adjunct. Tavartkiladze and colleagues have emphasized these convergences in translational frameworks linking melatonin to cancer risk, dysbiosis, and chronotherapy [12–16].

This review integrates three pillars. **Physiology:** synthesis, compartmentalization, receptor systems, and mitochondrial signaling. **Pathochemistry:** mechanisms by which melatonin modifies redox biology, mitochondrial dynamics, and apoptosis across disease states. **Immunogenetics:** human genetic variation in melatonin receptors and mitochondrial background, with practical implications for personalized dosing and timing. Five original figures (Figures 1–5) and five retained tables (Tables 1–5) are used to anchor this framework.

2. Melatonin Biosynthesis and Mitochondrial Localization

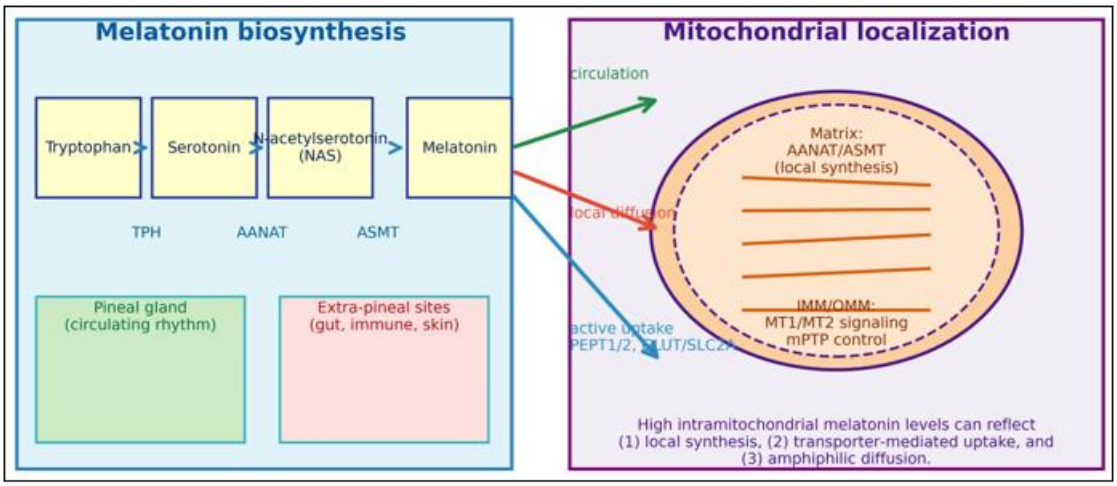
2.1 Canonical Biosynthesis: From Tryptophan to Melatonin

In humans, the canonical melatonin pathway proceeds from tryptophan to serotonin, then to N-acetylserotonin (NAS) via arylalkylamine N-acetyltransferase (AANAT), and finally to melatonin via acetylserotonin O-methyltransferase (ASMT). The pineal gland generates the best-characterized circadian rhythm of circulating melatonin, but extrapineal synthesis

occurs in multiple tissues—including the gastrointestinal tract, immune cells, and skin—where melatonin often functions in an autocrine or paracrine manner [10,12].

Although circadian timing remains central to melatonin's endocrine identity, mitochondrial biology reframes melatonin as a molecule whose actions may be local, rapid, and compartment-specific. A central implication is that the relevant melatonin concentration for mitochondrial protection is not necessarily the circulating plasma level, but the intramitochondrial pool reached through local synthesis, transporter-mediated uptake, and diffusion. These relationships are summarized in Figure 1.

Figure 1. Melatonin biosynthesis and mitochondrial localization in human cells. The scheme highlights canonical synthesis (tryptophan → serotonin → NAS → melatonin), extrapineal sources, and the routes by which melatonin can enrich the mitochondrial compartment (local synthesis, amphiphilic diffusion, and active uptake via PEPT1/2 and related transporters). Concepts are supported by mitochondrial melatonin literature [1–3,5–7,11].



2.2 Intramitochondrial Synthesis and Accumulation

Several observations support an intramitochondrial melatonin pool. First, mitochondria contain high concentrations of melatonin relative to cytosolic compartments in a range of models, consistent with local accumulation and retention [1,5,6]. Second, mitochondria may possess the enzymatic capacity to synthesize melatonin, and mitochondrial melatonin can act locally to prevent cytochrome c release in stress paradigms [3]. Third, dedicated membrane transport appears to contribute: human peptide transporters PEPT1/2 facilitate melatonin entry into mitochondria in cancer cells, with downstream effects on apoptosis and metabolism [11].

These findings suggest a practical principle for translational work: when melatonin is used as a mitochondrial protectant, the clinical question becomes the clinical question becomes not only about the dose required to raise plasma melatonin levels, but also "what intervention sustains an intramitochondrial melatonin concentration sufficient to stabilize the ETC and modulate permeability transition?" [1,5,6].

2.3 Receptor Systems and Signaling Relevant to Mitochondria

Melatonin signals through high-affinity G-protein–coupled receptors MT1 (encoded by MTNR1A) and MT2 (encoded by MTNR1B), and also interacts with additional binding partners—including the historically defined MT3 site, now widely linked to quinone reductase 2 (NQO2), and nuclear receptors such as RORα/RZR. While MT1/MT2 are classically plasma-membrane receptors, their signaling outputs (cAMP reduction, modulation of kinase pathways, and nitric oxide regulation) intersect mitochondrial metabolism and redox balance at multiple points [9,12].

Table 1 summarizes a pragmatic view of receptor-coupled signaling that is most often invoked when mitochondrial endpoints are measured (bioenergetics, ROS production, and permeability transition).

Table 1: Major melatonin receptor systems and canonical signaling outputs with mitochondrial relevance (retained from the source manuscript).

Receptor	G protein	Representative downstream effects (mitochondria-relevant)
MT1 (MTNR1A)	Gi/Gq	↓ cAMP; ↓ PKA; modulation of kinase signaling and mitochondrial function
MT2 (MTNR1B)	Gi	↓ cAMP; inhibition of nitric oxide synthase activity; vascular and metabolic signaling
RORα/RZR (nuclear)	—	Transcriptional regulation of antioxidant enzymes and inflammatory tone

3. Core Mitochondrial Functions Modulated by Melatonin

3.1 Antioxidant Actions in the Mitochondrial Compartment

The best-established mitochondrial action of melatonin is its antioxidant capacity. Melatonin is amphiphilic and can access lipid membranes and aqueous compartments, enabling it to intercept free radicals generated near ETC complexes and within cardiolipin-rich membranes. Importantly, melatonin acts both directly (as a radical scavenger) and indirectly (by upregulating endogenous antioxidant enzymes and downregulating pro-oxidant systems). A physicochemical analysis of melatonin's radical-scavenging behavior supports its broad reactivity across ROS/RNS species [7], while broader biological syntheses emphasize that mitochondrial localization magnifies these protective effects at the primary site of oxidant generation [1,5].

A distinctive feature is the so-called antioxidant cascade: melatonin metabolites such as AFMK and AMK retain radical-scavenging activity, allowing one parent molecule to neutralize multiple oxidants through sequential conversions [1,7]. In practical terms, melatonin may provide more antioxidant work per molecule than classic chain-breaking antioxidants that terminate after a single radical encounter. The cascade concept is illustrated in Figure 2.

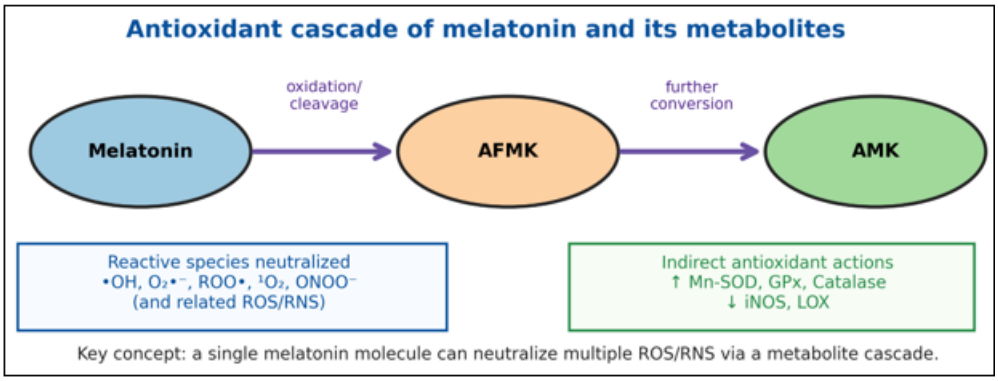


Figure 2: Antioxidant cascade of melatonin and its kynuric metabolites (AFMK and AMK). The cascade concept underlies the high radical-scavenging capacity attributed to melatonin in mitochondrial redox biology [1,7].

3.2 Electron Transport, Membrane Potential, and ATP Production

Melatonin influences bioenergetics by stabilizing electron transport, preserving mitochondrial membrane potential ($\Delta\Psi m$), and limiting electron leak that fuels superoxide formation. The net effect reported across diverse models is improved coupling efficiency and reduced oxidative injury, especially during ischemia–reperfusion–like stress or toxin exposure. In Reiter's formulation, melatonin "anticipates" mitochondrial stress by acting at multiple levels—scavenging radicals, preserving cardiolipin integrity, and reducing the probability of permeability transition [1,5].

Because mitochondrial damage is often patchy within a cell population, the functional outcome is frequently a shift in the distribution of mitochondrial states: fewer highly depolarized organelles, improved respiratory control ratios, and a reduced tendency toward bioenergetic collapse. These effects provide a mechanistic bridge between melatonin's molecular chemistry and clinically meaningful endpoints such as reduced tissue necrosis and improved recovery after oxidative insults. A consolidated view of these coordinated actions is provided in Figure 3.

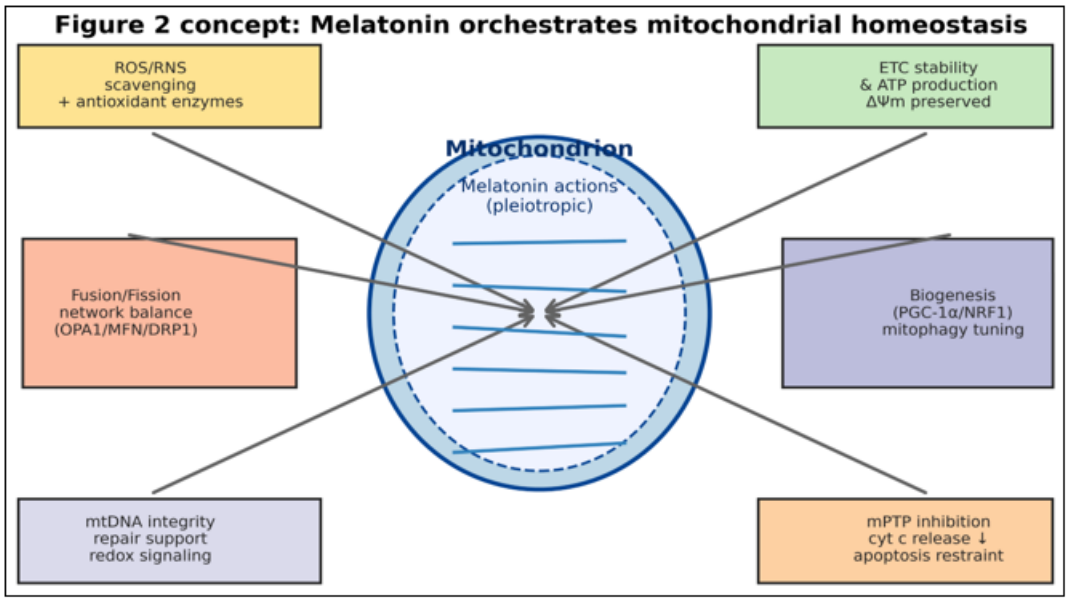


Figure 3: Melatonin orchestrates mitochondrial homeostasis through coordinated effects on redox balance, ETC stability, permeability transition, dynamics, mitophagy, and transcriptional control [1,3,5,6].

3.3 Permeability Transition, Cytochrome c Release, and Intrinsic Apoptosis

Mitochondria are gatekeepers of intrinsic apoptosis. A critical inflection point is the opening of the mitochondrial permeability transition pore (mPTP) and the consequent loss of ΔΨm, swelling, and release of cytochrome c. Experimental work has shown that mitochondrial melatonin can engage receptor-linked signaling pathways that block cytochrome c release, positioning melatonin as an upstream modulator of apoptotic commitment [3].

In cancer biology, this axis carries a dual interpretation. In normal tissues under inflammatory or ischemic stress, melatonin's antiapoptotic actions may be protective. In malignant cells, however, melatonin may promote apoptosis depending on context, dose, and transporter-mediated mitochondrial accumulation—an effect demonstrated in cancer-cell models with PEPT1/2-dependent uptake [11]. Thus, mitochondrial melatonin biology supports both cytoprotection and oncostatic activity without contradiction; the direction depends on the redox and metabolic context and on the integrity of apoptosis checkpoints.

3.4 Mitochondrial Dynamics, Network Integrity, and Mitophagy

Mitochondria form a dynamic network that continuously remodels by fusion and fission. Under sustained oxidative stress, excessive fission can fragment the network, promote ROS generation, and favor apoptosis. Conversely, fusion supports cristae integrity and ETC efficiency. Melatonin has been repeatedly associated with restoration of balanced dynamics and with improved quality control via mitophagy and biogenesis programs [1,5,19]. These relationships are schematized in Figure 4.

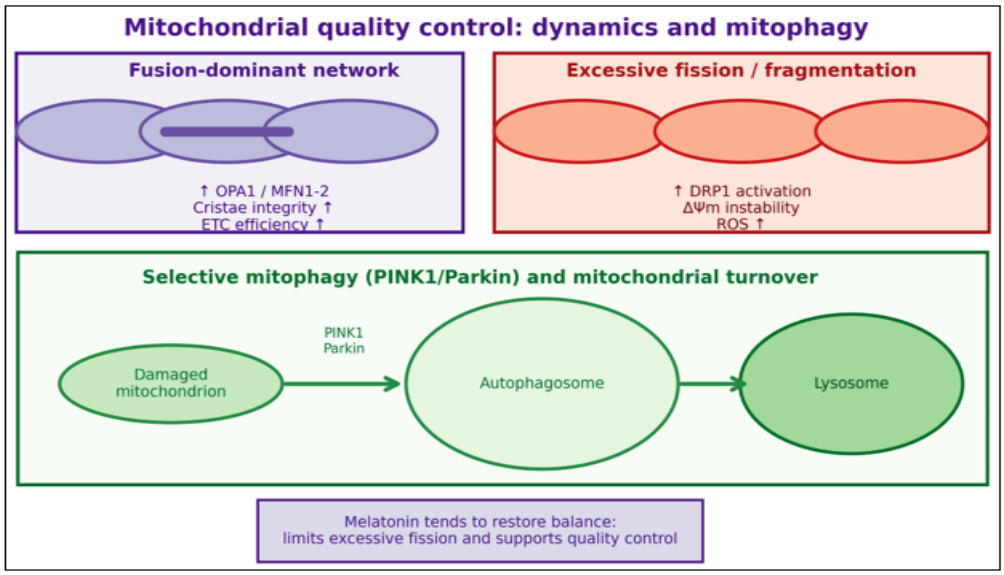


Figure 4: Mitochondrial quality control: fusion–fission balance and selective mitophagy. Melatonin is frequently reported to limit maladaptive fragmentation and to support homeostatic turnover, preserving cristae structure and bioenergetic resilience [1,5,19].

4. Pathochemistry of the Melatonin–Mitochondria Interface

4.1 Oxidative Damage, mtDNA Integrity, and Redox Signaling

Oxidative stress is not merely collateral damage; it is a chemical language that can remodel signaling networks, gene expression, and cell fate. Mitochondrial DNA (mtDNA) is particularly vulnerable because it is located near the ETC and lacks some of the protective histone architecture of nuclear DNA. Melatonin's mitochondrial enrichment therefore has two intertwined consequences: it can directly neutralize ROS/ RNS near their source, and it can shape redox-sensitive signaling pathways that govern inflammatory tone and repair capacity [1,5,8].

At low-to-moderate stress levels, redox signaling can be adaptive; at sustained high levels, it becomes destructive, driving lipid peroxidation, protein carbonylation, and mtDNA lesions. In this destructive regime, melatonin is repeatedly reported to reduce oxidative biomarkers and to improve cellular resilience—effects that are especially visible in tissues with high mitochondrial density (heart, brain, liver) [4–8].

4.2 Mitochondrial Permeability Transition and Bioenergetic Collapse

A common pathochemical endpoint across ischemia, toxin exposure, and inflammatory injury is the transition from manageable respiratory impairment to catastrophic failure: $\Delta\Psi m$ collapses, ATP production falls, and permeability transition commits cells to necrosis or apoptosis. Melatonin's ability to reduce oxidant load and modulate receptor-linked signaling that restrains cytochrome c release provides a plausible mechanism for delaying or preventing this collapse [1,3,5].

4.3 Cancer Metabolism, Mitochondria, and Oncostatic Context

Cancer cells frequently display metabolic reprogramming characterized by increased aerobic glycolysis (the Warburg phenotype), altered mitochondrial substrate utilization, and redox adaptations that support proliferation. Within this landscape, melatonin is of interest not only as an antioxidant but also as a metabolic and chronobiologic modulator. Tavartkiladze has argued that melatonin can be positioned as an adjuvant to cancer therapy, particularly when paired with time-aware strategies (chronotherapy) and with interventions targeting dysbiosis and inflammation [12–16].

Mechanistically, melatonin can constrain inflammatory signaling, influence mitochondrial function, and, in some contexts, favor apoptotic susceptibility of malignant cells—particularly when transporter-mediated mitochondrial uptake is efficient [11]. In parallel, chronotherapy approaches that restore circadian organization may improve tolerability and therapeutic response, with melatonin serving as both a signal of timing and a mitochondrial protectant [16].

4.4 Post-Viral Syndromes and Dysbiosis: Mitochondrial Consequences

Persistent fatigue and multisystem symptoms following viral infections have renewed interest in circadian disruption, chronic inflammation, and mitochondrial dysfunction. In an observational cohort framework, Tavartkiladze and colleagues described low melatonin in post-COVID syndrome and proposed that melatonin dysregulation and dysbiosis could promote oxidative stress and a pro-tumorigenic milieu [15]. While mechanistic causality requires controlled trials, the conceptual model is compatible with mitochondrial pathochemistry: sustained inflammation and altered microbial metabolites can impair mitochondrial function, while melatonin deficiency may remove a key mitochondrial defense layer.

4.5 Hepatic Metabolism, NAFLD, and Mitochondrial Redox Balance

The liver is a central organ of mitochondrial metabolism and is highly sensitive to redox imbalance. In NAFLD and related metabolic syndromes, mitochondrial dysfunction, ER stress, and inflammation form a self-reinforcing triad. Tavartkiladze has proposed that melatonin, integrated with microbiome-aware strategies and complementary phytochemicals, may reduce oxidative stress and inflammatory injury in fatty liver disease while potentially modifying cancer risk trajectories [14].

5. Immunogenetics and Precision Medicine

5.1 Why Genetics Matters for Melatonin–Mitochondria Biology

Inter-individual variability is a defining feature of melatonin responses in humans. Differences in receptor expression, downstream signaling efficiency, and melatonin metabolism can shift the balance between chronobiotic effects (sleep timing, circadian phase) and broader metabolic or mitochondrial endpoints. Genetic variation in melatonin receptors (MTNR1A/MTNR1B), melatonin synthesis enzymes (AANAT/ASMT), and drug-metabolizing enzymes (e.g., CYP1A2) therefore becomes relevant when melatonin is used as a targeted intervention rather than a general supplement.

In parallel, mtDNA haplogroup background can influence baseline ETC efficiency and ROS generation. This is not a claim that haplogroups determine health outcomes in isolation, but rather that mitochondrial background may shape the "redox reserve" on which melatonin acts. The tables below preserve the immunogenetic framing of the source manuscript and are intended as hypotheses and trial-design aids rather than deterministic clinical rules.

5.2 MTNR1A (MT1) Polymorphisms with Proposed Clinical Associations

MTNR1A variation can influence circadian signaling and has been explored in psychiatric and sleep-related phenotypes. Table 2 lists selected MTNR1A polymorphisms and the associations commonly cited in the literature (e.g.,

promoter polymorphism rs2119882 in insomnia phenotypes) [20].

Table 2: Selected MTNR1A polymorphisms and proposed phenotype associations (retained from the source manuscript; see also [19, 20]).

SNP	Genomic location	Reported / proposed association
rs2119882	Promoter region	Sleep disorders, depressive phenotypes (incl. insomnia associations in psychiatric cohorts)
rs6553010	Intron	Type 2 diabetes risk modulation (reported in some population studies)
rs2165666	Exon	Autism spectrum traits, ADHD (reported in neurodevelopmental genetics literature)

5.3 MTNR1B (MT2) Polymorphisms and Metabolic Phenotypes

Among melatonin receptor polymorphisms, MTNR1B variants have some of the strongest and most replicated associations with glucose regulation. In large genome-wide association analyses, rs10830963 has been linked to higher fasting glucose and to increased type 2 diabetes risk [17,18]. Promoter variation (including rs4753426) has been investigated in clinical cohorts [20]. Table 3 summarizes key MTNR1B variants relevant to metabolic phenotypes.

Table 3: Selected MTNR1B polymorphisms and proposed functional/clinical associations (retained from the source manuscript; see [17, 18, 20]).

SNP	Putative functional effect	Association / phenotype
rs10830963	G allele associated with higher fasting glucose; reduced β-cell function	Type 2 diabetes risk and impaired glucose homeostasis
rs1387153	Association with insulin secretion and glucose regulation	Prediabetes / insulin dysregulation phenotypes
rs4753426	Proposed influence on receptor expression	Gestational diabetes risk (reported in some cohorts)

5.4 mtDNA Haplogroups and Hypothesized Melatonin Responsiveness

Mitochondrial haplogroups reflect ancient population history and can correlate with subtle differences in oxidative phosphorylation efficiency and ROS production. Table 4 presents an illustrative hypothesis: haplogroups characterized by different baseline ETC behavior may show different "response surfaces" to melatonin's mitochondrial actions. This concept should be tested in prospective pharmacogenomic trials.

Table 4: Illustrative mitochondrial haplogroups and hypothesized functional tendencies (retained from the source manuscript).

Haplogroup	General mitochondrial tendency (hypothesis)	Hypothesized melatonin sensitivity
H	Higher oxidative phosphorylation efficiency	Moderate responsiveness
J	Lower ROS generation and distinct ETC coupling	Potentially higher responsiveness
T	Intermediate / mixed bioenergetic profile	Moderate responsiveness
U	Reduced ATP generation in some reports	Potential benefit in mitochondrial support contexts
Other	Variable	Requires empirical assessment

5.5 Pharmacogenetic Considerations and Decision Support

Genotype-informed dosing is still an emerging concept for melatonin, but it is a logical extension of receptor genetics and metabolism. Table 5 provides example considerations that may be operationalized in clinical research protocols, particularly when melatonin is used for metabolic indications or in combination oncology regimens where mitochondrial protection and chronobiology are both relevant.

Table 5: Illustrative genotype-informed considerations for melatonin use (retained from the source manuscript; intended for research protocols).

Genotype / marker	Potential implication for melatonin intervention
MTNR1B rs10830963 (GG)	Higher baseline diabetes risk: monitor glucose; consider avoiding late-evening melatonin with meals; personalize timing
MTNR1A rs2119882 (CC)	Potentially higher receptor sensitivity: consider lower starting dose; monitor sleep architecture and mood effects
CYP1A2 fast metabolizer	Faster clearance: may require higher dose or modified timing to sustain effect

5.6 An Integrated Framework for Precision Chronobiology and Mitochondrial Protection

Figure 5 summarizes a pragmatic framework for future trials: receptor genotype and mitochondrial background are combined with circadian phenotype and disease context to guide melatonin timing (chronotherapy) and dose. This approach is aligned with Tavartkiladze's emphasis on integrating circadian biology with metabolic and inflammatory phenotypes in cancer and post-viral syndromes [12–16].

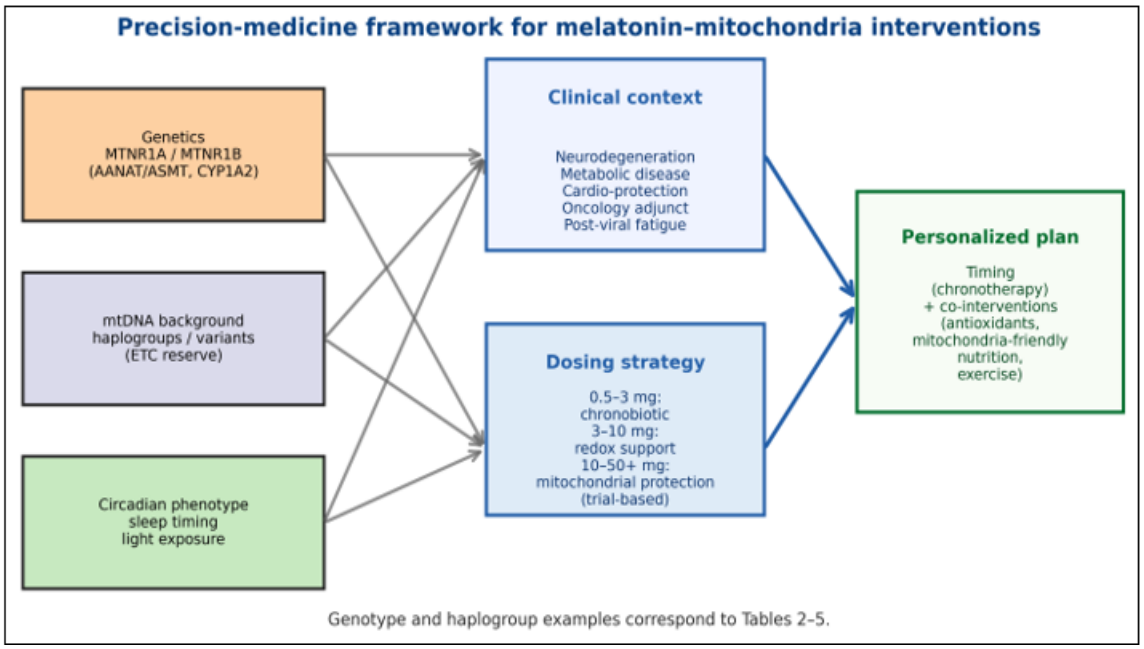


Figure 5: Precision-medicine framework for melatonin–mitochondria interventions. Genotype (Tables 2–3), mtDNA background (Table 4), and metabolism markers (Table 5) can be combined with circadian phenotype and clinical indication to personalize timing and dose [12–18].

6. Clinical and Translational Implications

6.1 Timing and Dose: Chronobiotic versus Mitochondria-Targeted Use

Melatonin has at least two therapeutic "modes" that can overlap but should not be conflated. The first is the chronobiotic mode, in which low doses timed to the biological evening shift circadian phase and improve sleep onset. The second is the mitochondria-targeted cytoprotective mode, in which melatonin is deployed as an antioxidant and bioenergetic stabilizer under conditions of oxidative injury. The Reiter literature emphasizes that mitochondrial endpoints may require higher exposures than those used for sleep timing, because the goal is to saturate mitochondrial compartments and sustain an intramitochondrial pool [1,5,6].

From a precision-medicine perspective, timing should be informed by the indication. For metabolic phenotypes linked to MTNR1B variation, the relationship between melatonin signaling and insulin secretion suggests careful attention to the timing of melatonin relative to meals and to endogenous circadian phase [17,18]. In oncology and post-viral syndromes, a trial framework may explicitly test whether circadian alignment plus mitochondrial protection yields additive benefit—an approach advocated in Tavartkiladze's chronotherapy and dysbiosis-oriented models [12–16].

6.2 Biomarkers and Mitochondrial Endpoints for Human Studies

Human trials that claim "mitochondrial effects" should incorporate mitochondrial endpoints rather than relying solely on symptom scales. Candidate biomarkers include circulating markers of oxidative stress and inflammation, mitochondrial respiration in peripheral blood mononuclear cells, mtDNA copy number or damage proxies, and metabolomic signatures reflecting NAD+/NADH balance and lactate handling. In addition, chronobiologic measures (dim-light melatonin onset, actigraphy, light exposure) are necessary to separate circadian from non-circadian effects.

6.3 Future Directions: Mitochondria-Targeted Melatonin and Combination Strategies

Several future directions stand out. First, mitochondria-targeted melatonin analogs or delivery systems may improve compartmentalization and reduce inter-individual variability in uptake. Second, combination strategies that couple melatonin with agents that restore mitochondrial dynamics, improve NAD+ metabolism, or reduce inflammatory tone could be rationally designed using the mechanistic map in Figure 3. Third, the microbiota–tryptophan–melatonin axis offers a systems-level lever: diet- and microbiome-based interventions may modulate host melatonin pathways and mitochondrial function simultaneously, a theme developed in Tavartkiladze and Reiter's recent synthesis [12,13].

7. Conclusions

Melatonin's relationship with mitochondria is no longer a peripheral observation; it is a coherent explanatory framework that links molecular chemistry to cellular fate and, potentially, to clinical outcomes. By accumulating within mitochondria, melatonin can blunt oxidative stress at its source, stabilize electron transport, and reduce the probability of permeability transition. By influencing dynamics and quality control, it can preserve a healthy mitochondrial network and improve bioenergetic resilience. Finally, receptor genetics and mitochondrial background invite a precision-medicine approach in which melatonin is timed and dosed according to circadian phenotype, metabolic risk, and mitochondrial vulnerability. Carefully designed trials—anchored in mitochondrial endpoints and informed by immunogenetics—are now required to translate

this mature mechanistic literature into standardized clinical practice.

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