

Review Article

Inherited Mitochondrial Genetics as a Predictor of Immune Checkpoint Inhibition Efficacy in Melanoma: A Narrow Review

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Abstract: The advent of immune checkpoint inhibitors (ICIs) has transformed melanoma treatment, offering durable responses for a subset of patients. Yet, considerable interpatient variability in therapeutic efficacy underscores the need for more precise predictive biomarkers. While most research has focused on nuclear genomic features such as PD-L1 expression and tumor mutational burden, emerging studies highlight a critical role for inherited mitochondrial genetics in shaping immune responses. Mitochondrial DNA (mt DNA) variants influence key immunologic processes, including T cell metabolism, reactive oxygen species production, and antigen presentation. This review explores the current landscape of mitochondrial genomics in the context of melanoma immunotherapy, examining how mt DNA haplogroups and mutations may affect ICI responsiveness. By elucidating the intersection between mitochondrial biology and immune modulation, this work advocates for the integration of mitochondrial genotyping into future biomarker strategies to enhance patient stratification and improve therapeutic outcomes.

Keywords: inherited, mitochondrial genetics, immune checkpoint, inhibition efficacy

1. INTRODUCTION

Melanoma, a notably immunogenic malignancy of the skin, has demonstrated remarkable improvements in patient outcomes with the advent of immune checkpoint inhibitors (ICIs), particularly those targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways. Despite these therapeutic advancements, a substantial proportion of patients exhibit primary or acquired resistance to ICIs, or develop significant immune-related adverse events [1]. Consequently, the identification of predictive biomarkers and the development of personalized immunotherapeutic strategies have become critical priorities within the field of immuno-oncology. While extensive research has elucidated tumor-intrinsic determinants of ICI response—such as tumor mutational burden and the integrity of antigen presentation pathways—mitochondrial genomics has only recently garnered attention as a pivotal modulator of immune competence. Beyond their canonical role in cellular bioenergetics, mitochondria serve as central regulators of innate immune signaling, redox homeostasis, and T cell fate decisions [2]. This review critically examined the emerging evidence linking germline mitochondrial genetic variation to differential responses to ICIs in melanoma, thereby highlighting a novel and potentially actionable axis of immunotherapeutic modulation.

2. MITOCHONDRIAL FUNCTION AND IMMUNITY: A BIOLOGIC OVERVIEW

Traditionally recognized for their pivotal roles in cellular energy metabolism and the regulation of apoptosis, mitochondria have recently emerged as central modulators of immune function. Far beyond their classical bioenergetic functions, mitochondria orchestrate a range of immunological processes essential for both innate and adaptive immunity. These include the regulation of inflammasome

activation, generation of reactive oxygen species (ROS), calcium homeostasis, and the production of adenosine triphosphate (ATP)—all of which are critical to the activation, differentiation, and effector responses of T lymphocytes [3]. Importantly, mitochondrial metabolic reprogramming serves as a hallmark of T cell functional states: naïve T cells predominantly depend on oxidative phosphorylation (OXPHOS) for energy generation, while upon activation, they undergo a metabolic shift toward aerobic glycolysis, also known as the Warburg effect, to meet the biosynthetic demands of rapid proliferation and effector molecule synthesis. Beyond metabolism, mitochondrial integrity plays a crucial role in shaping immune responses. Mitochondrial stress, depolarization of the mitochondrial membrane potential, and the release of mitochondrial components—particularly mitochondrial DNA (mt DNA)—into the cytosol can serve as potent danger-associated molecular patterns (DAMPs) [4]. These events trigger the activation of cytosolic DNA sensors, most notably the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway. This signaling cascade leads to the induction of type I interferon responses and pro-inflammatory cytokine production, thereby influencing both local and systemic immune activation. Moreover, mitochondrial-derived ROS can further enhance inflammatory signaling through activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and other transcriptional pathways critical to immune cell function [5]. Genetic variability in mitochondrial DNA, as well as in nuclear-encoded genes involved in mitochondrial maintenance and function, introduces an additional layer of complexity. Polymorphisms in these genes may modulate mitochondrial bioenergetics, dynamics (including fission and fusion), and stress responses, thereby altering the immune system's capacity to mount effective antitumor responses. Emerging evidence suggests that such genetic variants can influence the threshold for immune cell activation, the durability of T cell responses, and the overall efficacy of immune checkpoint inhibitors (ICIs). In this context, the mitochondrial genome—and by extension, mitochondrial function—represents a previously underappreciated but potentially critical determinant of immunotherapeutic outcomes in cancer patients [6]. Elucidating these relationships through integrative analyses of mitochondrial genomics, immunometabolism, and clinical response data may pave the way for more precise biomarker development and the rational design of combination therapies aimed at overcoming resistance to ICIs.

3. GENETIC VARIATIONS IN MITOCHONDRIAL DNA

Mitochondrial DNA (mt DNA) is a unique, maternally inherited, double-stranded circular genome that resides within the mitochondrial matrix. It spans approximately 16.5 kilobases and encodes 13 essential polypeptides of the oxidative phosphorylation (OXPHOS) system, in addition to 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs), which are necessary for the organelle's autonomous protein synthesis. Unlike nuclear DNA, mt DNA lacks protective histones and is situated in close proximity to the electron transport chain, where high levels of reactive oxygen species (ROS) are generated as byproducts of aerobic respiration [7]. This spatial relationship, coupled with relatively inefficient DNA repair mechanisms within mitochondria, results in a mutation rate that is markedly higher than that observed in nuclear genomic DNA. Consequently, mt DNA exhibits a broad spectrum of sequence variations, some of which have been evolutionarily selected and grouped into phylogenetically distinct haplogroups. These mitochondrial haplogroups, which reflect ancient maternal lineages, have been shown to influence a variety of mitochondrial functions, including electron transport efficiency, ROS production, calcium handling, and susceptibility to apoptosis [8]. Importantly, variations in mt DNA haplotypes can also modulate cellular metabolism and redox balance, thereby indirectly influencing immune cell function and inflammatory responses. In the context of cancer, particularly melanoma—a malignancy characterized by pronounced immunogenicity and metabolic plasticity—emerging studies suggest that specific mt DNA haplogroups may play a determinative role in shaping patient responses to immune checkpoint inhibitors (ICIs). Mechanistically, these associations may be mediated through haplotype-dependent alterations in mitochondrial metabolism, antigen presentation efficacy, and

innate immune signaling pathways such as cGAS–STING activation in response to mitochondrial stress [9]. For example, certain haplogroups associated with increased oxidative stress or diminished mitochondrial function may lead to impaired T cell activation or dysregulated immune surveillance, thereby reducing the efficacy of ICIs. Conversely, haplotypes that support more robust mitochondrial metabolism and redox homeostasis may enhance antitumor immunity and therapeutic responsiveness. These findings underscore the relevance of mitochondrial genomic background as a potential biomarker for immunotherapy stratification [10]. Incorporating mtDNA haplogroup analysis into clinical and translational research could therefore provide novel insights into interindividual variability in ICI outcomes and facilitate the development of more personalized and effective treatment strategies for melanoma and other malignancies.

4. MITOCHONDRIAL DYSFUNCTION IN TUMOR AND IMMUNE CELLS

Tumor cells are characterized by marked metabolic plasticity, enabling them to adapt to fluctuating environmental and nutrient conditions. While the Warburg effect—an increased reliance on aerobic glycolysis even in the presence of oxygen—remains a metabolic hallmark of many malignancies, including melanoma, mitochondrial function remains indispensable for tumor cell survival, particularly under conditions of metabolic or oxidative stress [11]. Mitochondria support critical biosynthetic pathways, redox balance, and apoptotic resistance, thereby contributing to tumor progression and therapeutic resistance. In contrast, the metabolic requirements of immune cells, particularly T lymphocytes, are distinct and dynamically regulated across activation states. Naïve and memory T cells depend heavily on mitochondrial oxidative phosphorylation (OXPHOS) to maintain long-term survival and functional integrity, whereas effector T cells transiently shift toward glycolysis to sustain rapid proliferation and cytotoxic activity [12]. The functional integrity of mitochondria within T cells is increasingly recognized as a central determinant of antitumor immunity. Robust mitochondrial health is critical for the formation and persistence of memory T cells, efficient cytokine production, and sustained immune surveillance. Conversely, mitochondrial dysfunction within tumor-infiltrating lymphocytes (TILs) is closely associated with features of T cell exhaustion, including decreased proliferative capacity, impaired effector function, altered transcriptional programming, and diminished metabolic fitness [13]. These impairments correlate strongly with resistance to immune checkpoint inhibitors (ICIs), as exhausted or metabolically compromised T cells are less capable of responding to PD-1 or CTLA-4 blockade. Notably, inherited deficiencies in mitochondrial function—whether due to germline polymorphisms in mtDNA or in nuclear-encoded mitochondrial maintenance genes—may precondition the immune system toward suboptimal responsiveness. Such inherited variants could shape the immunometabolism landscape of the tumor microenvironment (TME) by impairing T cell fitness even before therapeutic intervention. A TME dominated by energetically compromised or senescent T cells is less amenable to reactivation via checkpoint blockade, thereby contributing to primary resistance [14]. These insights highlight the potential of mitochondrial genomic profiling as a prognostic or predictive tool in immunotherapy, offering a new dimension to personalized cancer treatment strategies. Future research elucidating the interplay between host mitochondrial genetics, T cell metabolism, and therapeutic responsiveness will be essential to refine immunotherapeutic paradigms.

5. INHERITED MITOCHONDRIAL POLYMORPHISMS AND CANCER SUSCEPTIBILITY

A growing body of evidence has linked mitochondrial DNA (mtDNA) variants to both cancer susceptibility and disease progression, underscoring the biological relevance of mitochondrial genomics in oncogenesis. Specific mtDNA haplogroups—defined by phylogenetic clusters of inherited polymorphisms—exhibit distinct bioenergetic and oxidative stress profiles, which can modulate cellular susceptibility to transformation [15]. For instance, haplogroup J, which is prevalent in European

populations, has been associated with increased mitochondrial ROS production and diminished electron transport chain efficiency. These metabolic characteristics are thought to contribute to enhanced oxidative DNA damage and genomic instability, thereby increasing the risk for a range of oxidative stress–related malignancies, including colorectal, prostate, and thyroid cancers [16]. In the context of melanoma, several mt DNA regions have emerged as potential hotspots for oncogenic influence. Variations within the displacement-loop (D-loop) region, a non-coding but highly regulatory segment involved in mt DNA replication and transcription, have been implicated in increased mt DNA mutation rates and altered mitochondrial function [17]. Similarly, mutations in the mitochondrial NADH dehydrogenase (MT-ND) gene family—particularly MT-ND1, MT-ND4, and MT-ND5—have been reported to affect respiratory chain activity, ROS balance, and apoptotic resistance in melanoma cells. These alterations can contribute not only to tumorigenesis but also to the development of an immunosuppressive tumor microenvironment. Importantly, such mt DNA variants may extend their influence beyond tumor initiation and progression to affect therapeutic outcomes, particularly in the setting of immune checkpoint inhibitor (ICI) therapy. By modulating mitochondrial metabolism, ROS signaling, and innate immune activation pathways, these inherited and somatic mitochondrial alterations may directly shape the capacity of immune cells to mount effective antitumor responses [18]. For example, elevated ROS levels can impair T cell viability and function, while altered mt DNA content or sequence may influence the immunogenicity of tumor cells and the activation of pattern recognition receptors such as toll-like receptors (TLRs) or the c GAS–STING axis. Thus, mt DNA variants may serve as dual biomarkers—reflecting both melanoma susceptibility and responsiveness to immunotherapy. Collectively, these findings support the integration of mitochondrial genomic analysis into comprehensive molecular profiling strategies aimed at optimizing cancer risk prediction, prognostication, and treatment personalization in melanoma. Further large-scale, multi-ethnic studies are warranted to validate these associations and to uncover novel mt DNA signatures predictive of ICI response.

6. MITOCHONDRIAL INFLUENCE ON TUMOR MICROENVIRONMENT (TME)

The tumor microenvironment (TME) represents a dynamic and heterogeneous ecosystem comprising malignant cells, stromal fibroblasts, endothelial cells, extracellular matrix components, and a diverse repertoire of infiltrating immune cells. Within this milieu, mitochondrial function—across both tumor and immune compartments—plays a pivotal role in shaping the immunological tone and determining the success or failure of antitumor immune responses [19]. Mitochondrial dysfunction within the TME contributes to an immunosuppressive landscape through several interconnected mechanisms, including metabolic reprogramming, hypoxia, and immune cell polarization. One major consequence of mitochondrial dysregulation in tumor cells is the preferential reliance on glycolysis for energy production, even in the presence of oxygen—a phenomenon known as the Warburg effect. This metabolic shift results in excessive lactic acid accumulation, which lowers extracellular pH and creates a metabolically hostile environment for effector immune cells [20]. Acidification of the TME has been shown to impair cytotoxic T lymphocyte (CTL) proliferation, cytokine secretion, and motility, while favoring the expansion and function of immunosuppressive subsets such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Concurrently, mitochondrial dysfunction exacerbates tumor hypoxia, which further dampens immune activation by stabilizing hypoxia-inducible factors (HIFs) that promote immune evasion and angiogenesis [11]. Moreover, mitochondrial-derived reactive oxygen species (ROS) have been implicated in modulating antigen presentation and shaping cytokine secretion profiles within the TME. Elevated ROS levels can disrupt the function of antigen-presenting cells (APCs), alter the expression of major histocompatibility complex (MHC) molecules, and skew cytokine production toward an anti-inflammatory profile, thereby blunting the activation and expansion of tumor-reactive T cells [14]. These alterations can significantly compromise the efficacy of immune

checkpoint inhibitors (ICIs), which depend on the reinvigoration of pre-existing or newly primed antitumor immune responses. Crucially, patients harboring inherited mt DNA polymorphisms that influence mitochondrial metabolism, ROS production, or stress signaling pathways may exhibit variable immunological phenotypes within the TME. Depending on the functional consequence of these genetic variants, individuals may experience either enhanced immune surveillance and responsiveness to ICIs or, conversely, increased resistance due to a predisposition toward immunosuppressive metabolic reprogramming [9]. For instance, mt DNA variants that impair mitochondrial respiration may lead to increased glycolytic flux and lactic acid accumulation, while others may modulate redox balance in ways that favor immune activation. These findings underscore the importance of considering host mitochondrial genomic background as a critical, yet often overlooked, factor in determining the immunogenicity of the TME and the clinical response to checkpoint blockade [18]. Future investigations integrating mitochondrial genotyping with metabolic and immunological profiling of the TME could enable the identification of predictive biomarkers and the development of tailored therapeutic interventions that target mitochondrial pathways to overcome ICI resistance.

7. PRECLINICAL EVIDENCE LINKING MITOCHONDRIAL GENOTYPE TO ICI RESPONSE

Preclinical studies utilizing murine models have been instrumental in elucidating the mechanistic relationship between mitochondrial genetics, T cell metabolism, and responsiveness to immune checkpoint inhibitors (ICIs). Genetically engineered mouse models with targeted disruptions in key mitochondrial regulatory genes have revealed the profound impact of mitochondrial dysfunction on T cell-mediated immunity and antitumor responses. For instance, mice harboring T cell-specific deletions or mutations in *Tfam* (mitochondrial transcription factor A), a gene essential for mt DNA replication and maintenance, demonstrate impaired mitochondrial biogenesis, disrupted oxidative phosphorylation (OXPHOS), and defective T cell activation [12]. Similarly, mutations in *Polg* (the gene encoding the mitochondrial DNA polymerase gamma) lead to accelerated accumulation of mt DNA mutations and compromised mitochondrial function, resulting in decreased effector T cell fitness and reduced anti-tumor immunity. Another key regulator, *Cox10*, which is required for the assembly of cytochrome c oxidase (complex IV of the electron transport chain), has also been implicated in maintaining T cell bioenergetic integrity [16]. Conditional knockout of *Cox10* in T cells impairs mitochondrial respiration, leading to altered cytokine production, diminished proliferation, and a failure to sustain cytotoxic responses in the tumor microenvironment. These findings underscore the indispensable role of intact mitochondrial respiration and dynamics in supporting the metabolic reprogramming required for effective T cell function during immunotherapy. In addition to genetic models, recent advances in CRISPR/Cas9 genome editing have enabled precise manipulation of mitochondrial genes in both T cells and tumor cells, providing further insights into how mitochondrial competency influences immune responsiveness. For example, CRISPR-mediated editing of mitochondrial regulators has been used to either disrupt or enhance specific mitochondrial pathways, resulting in altered sensitivity to PD-1 or CTLA-4 blockade [13]. Tumor cells with compromised mitochondrial metabolism may exhibit reduced immunogenicity or increased resistance to T cell-mediated killing, while T cells with enhanced mitochondrial fitness demonstrate superior expansion, persistence, and functional capacity in response to checkpoint inhibition. Collectively, these murine studies provide compelling evidence that mitochondrial competence is a critical determinant of durable ICI efficacy. They support a conceptual framework wherein mitochondrial integrity governs both the immunogenic profile of tumor cells and the functional robustness of effector T cells [6]. These findings further justify the exploration of host and tumor mitochondrial genomics as potential predictive biomarkers and therapeutic targets in the context of cancer immunotherapy. Ongoing and future research integrating mitochondrial editing technologies with immuno-oncology platforms will be essential to validate these findings and to translate them into clinically actionable strategies.

8. CLINICAL STUDIES IN MELANOMA: EARLY INSIGHTS

Emerging retrospective analyses from clinical cohorts of melanoma patients treated with immune checkpoint inhibitors (ICIs) have begun to uncover potential associations between mitochondrial haplogroups and therapeutic outcomes. These preliminary findings suggest that germline mitochondrial genomic variation may serve as a novel determinant of immunotherapy response. In one such study, patients classified within mitochondrial haplogroup **H**—the most common haplogroup in European populations—exhibited significantly longer progression-free survival (PFS) following anti-PD-1 or anti-CTLA-4 therapy compared to those belonging to haplogroups J or U, which are characterized by distinct mitochondrial bioenergetic and oxidative stress profiles [5]. Haplogroup H has been associated with more efficient electron transport chain function and lower reactive oxygen species (ROS) production, potentially supporting more favorable immunometabolism conditions for T cell activation and persistence. Beyond haplogroup-level associations, specific mt DNA single nucleotide polymorphisms (SNPs) have also been correlated with differential immune phenotypes. Tumor biopsies from individuals harboring distinct mt DNA variants showed varying degrees of tumor-infiltrating lymphocytes (TILs), particularly CD8⁺ T cells, as well as differential expression of immune checkpoint molecules such as PD-1, PD-L1, and LAG-3. These observations raise the possibility that mt DNA variants may influence not only the intrinsic properties of immune cells but also the broader tumor immune microenvironment, through mechanisms involving metabolic crosstalk, ROS signaling, and antigen presentation capacity [8]. While these retrospective studies are inherently limited by small sample sizes, population stratification, and lack of functional validation, they collectively highlight the emerging predictive value of mitochondrial genomics in immuno-oncology [4]. The consistent directionality of observed associations across independent cohorts, despite their modest scale, provides a compelling rationale for prospective validation in larger, ethnically diverse patient populations. Moreover, integration of mt DNA sequencing into existing multi-omics platforms may enable more nuanced biomarker discovery efforts, particularly when combined with immunohistochemistry, transcriptomic profiling, and T cell receptor (TCR) repertoire analysis. In summary, these early clinical investigations underscore the translational potential of mitochondrial haplogroup and SNP analysis as predictive biomarkers of ICI efficacy in melanoma. Further research is warranted to elucidate the mechanistic underpinnings of these associations and to determine whether mitochondrial profiling can inform patient stratification, therapeutic decision-making, or the design of combination regimens that target immunometabolism vulnerabilities.

9. INTEGRATED GENOMIC APPROACHES: NUCLEAR-MITOCHONDRIAL CROSSTALK

Although mitochondrial DNA (mt DNA) encodes a limited subset of mitochondrial proteins, the vast majority—estimated at over 1,000 proteins—are encoded by nuclear genes and imported into the mitochondria post-translationally. These nuclear-encoded mitochondrial genes (NEMGs) are critical for maintaining mitochondrial biogenesis, dynamics (fission and fusion), mitophagy, redox regulation, and metabolic homeostasis [19]. Mutations or polymorphisms within NEMGs can profoundly influence mitochondrial structure and function, often with cascading effects on cellular energy metabolism and immune competence. Recent integrated genomic analyses that simultaneously evaluate both nuclear and mitochondrial genomic variation have begun to illuminate the complex interplay between these two genetic compartments in determining the outcomes of immune checkpoint inhibitor (ICI) therapy. By capturing the full spectrum of mitochondrial influence—from mt DNA-encoded core respiratory chain subunits to nuclear-encoded regulatory machinery—such approaches offer a more holistic understanding of how mitochondrial biology shapes antitumor immunity [15]. Notably, specific mutations in nuclear genes governing key mitochondrial pathways—such as mitophagy (e.g., PINK1, PRKN), apoptosis (e.g., BCL2 family genes), and metabolic regulation (e.g., SIRT3, ACO2, SDHA)—have

been implicated in modulating immune responsiveness to ICIs. These genes can affect the removal of damaged mitochondria, the sensitivity of cells to apoptotic signaling, and the overall bioenergetic state of immune cells, particularly T lymphocytes. When occurring in conjunction with functionally significant mt DNA variants, such nuclear mutations may act synergistically to amplify or attenuate mitochondrial dysfunction, thereby influencing T cell exhaustion, cytokine production, and memory formation—parameters critical for durable ICI response. For example, impaired mitophagy resulting from NEMG mutations may exacerbate the accumulation of dysfunctional mitochondria and elevated ROS levels, which can alter antigen presentation, damage effector T cells, and promote immunosuppressive signaling [12]. Conversely, nuclear variants that enhance mitochondrial resilience or support metabolic flexibility may potentiate the beneficial effects of ICI therapy, particularly in metabolically constrained tumor microenvironments. These emerging findings underscore the value of dual-compartment mitochondrial genomics in biomarker discovery and therapeutic stratification. Future studies leveraging multi-omics platforms—including whole exome sequencing, mitochondrial genome sequencing, transcriptomics, and immunometabolism profiling—will be essential to delineate the interactive effects of NEMGs and mt DNA on ICI outcomes [10]. Ultimately, the integration of nuclear and mitochondrial genomic data may enable the identification of combinatorial mitochondrial signatures predictive of treatment response, resistance, or toxicity, and inform the development of rational co-targeting strategies in cancer immunotherapy.

10. BIOMARKER DEVELOPMENT AND PREDICTIVE MODELING

An ideal biomarker for predicting response to immune checkpoint inhibitors (ICIs) should meet several critical criteria: biological stability, ease of accessibility, and a mechanistic relationship to immune regulation and therapeutic efficacy. In this context, mitochondrial haplogroups—defined by conserved, maternally inherited mt DNA polymorphisms—emerge as promising candidates [11]. Haplogroups are highly stable across an individual's lifetime, do not undergo somatic recombination, and can be readily identified through non-invasive peripheral blood sampling. These features make them particularly attractive for incorporation into clinical workflows, where minimally invasive, cost-effective biomarkers are essential for broad implementation. Unlike many single-point biomarkers, mitochondrial haplogroups reflect evolutionary adaptations in mitochondrial metabolism and redox biology, traits that are intimately linked to both tumor immunogenicity and immune cell functionality. This biological plausibility reinforces their potential as mechanistically meaningful predictors of immunotherapy response. However, mitochondrial biomarkers are unlikely to function in isolation [13]. Their predictive value may be substantially enhanced when integrated with existing immuno-oncologic biomarkers, such as programmed death-ligand 1 (PD-L1) expression, tumor mutational burden (TMB), and neoantigen load—factors known to reflect the likelihood of T cell recognition and reinvigoration upon checkpoint blockade. To harness the full predictive potential of these multi-dimensional datasets, researchers have increasingly turned to machine learning (ML) and artificial intelligence (AI)–based models. These computational frameworks are capable of identifying complex, non-linear relationships between mitochondrial genomic features and other layers of molecular, clinical, and immune profiling data. Recent studies using ML approaches have demonstrated improved accuracy in stratifying patients into ICI responders and non-responders when mt DNA signatures are incorporated alongside conventional biomarkers [21]. For example, predictive algorithms trained on integrated datasets have identified combinatorial mitochondrial-nuclear genotypes, gene expression patterns, and immune infiltration signatures that correlate strongly with progression-free and overall survival in melanoma cohorts. As the volume of multi-omics data from immunotherapy-treated patients continues to grow, the integration of mitochondrial haplogroup information within computational prediction pipelines holds considerable promise for refining patient selection and guiding treatment decisions. Moreover, these approaches may uncover previously unrecognized gene-environment-microbiome interactions

that shape the immunometabolism landscape and influence therapeutic outcomes. In sum, mitochondrial haplogroups represent a biologically relevant, stable, and clinically accessible biomarker class that may augment the predictive power of existing models. Their incorporation into integrative, AI-driven precision oncology platforms could pave the way for more individualized immunotherapy regimens and improved clinical outcomes.

11. CONCLUSION

Inherited mitochondrial genetics represent a promising, yet largely underexplored, frontier in the search for predictive biomarkers of immune checkpoint inhibitor (ICI) efficacy in melanoma. Unlike many tumor-intrinsic or circulating biomarkers that fluctuate over time or vary with disease stage, mitochondrial DNA (mt DNA) variants—particularly those that define stable haplogroups—offer a unique window into inherited immunometabolism predispositions. Through their multifaceted influence on cellular energy metabolism, reactive oxygen species (ROS) production, antigen presentation, and T cell functionality, mt DNA polymorphisms can shape the tumor–immune interface in ways that either enhance or impede the therapeutic activity of ICIs. Accumulating evidence from preclinical models, retrospective clinical analyses, and integrative genomic studies suggests that mitochondrial genotype can modulate both the immune microenvironment and the metabolic resilience of effector lymphocytes—two key determinants of response to PD-1 and CTLA-4 blockade. For instance, mitochondrial dysfunction has been shown to promote T cell exhaustion, lactic acidosis, and hypoxia within the tumor microenvironment (TME), all of which can undermine ICI efficacy. Conversely, mitochondrial competence supports memory T cell formation, pro-inflammatory signaling, and immune cell persistence—hallmarks of successful immunotherapy. Furthermore, the synergistic effects of nuclear-encoded mitochondrial gene (NEMG) variants and mt DNA mutations may amplify or mitigate these immunological consequences, underscoring the need for a dual-compartment approach to mitochondrial biomarker discovery. As immunotherapy continues to redefine the therapeutic landscape for advanced melanoma, there is a pressing need to refine predictive tools that can identify patients most likely to benefit from treatment while sparing others from unnecessary toxicity and cost. In this regard, mitochondrial genomics holds significant translational potential. Non-invasive detection of mt DNA haplotypes, when integrated with established biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and immune cell infiltration profiles, may enhance patient stratification and guide rational combination therapies. The incorporation of machine learning approaches further expands the possibilities, allowing the integration of complex, multilayered datasets into predictive models with high clinical utility. In summary, a deeper mechanistic and translational understanding of mitochondrial influences on immune regulation could pave the way for a new class of biomarkers and therapeutic targets in melanoma. The inclusion of mitochondrial genomics into the broader immuno-oncology framework not only enriches our understanding of treatment heterogeneity but also represents a critical step toward truly personalized cancer immunotherapy. Future large-scale, prospective studies integrating mitochondrial and nuclear genomic data with functional immune metrics will be essential to validate these findings and to unlock the full potential of mitochondrial biology in the era of precision oncology.

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