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REVIEWS

Exploiting the tumor immune microenvironment and immunometabolism using mitochondria-targeted drugs: Challenges and opportunities in racial disparity and cancer outcome research

Balaraman Kalyanaraman[1,2]

[1]Department of Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[2]Center for Disease Prevention Research, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Correspondence
Balaraman Kalyanaraman, Department of Biophysics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA.
Email: balarama@mcw.edu

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Abstract

Black and Hispanic cancer patients have a higher incidence of cancer mortality. Many factors (e.g., socioeconomic differences, insufficient access to healthcare) contribute to racial disparity. Emerging research implicates biological disparity in cancer outcomes. Studies show distinct differences in the tumor immune microenvironment (TIME) in Black cancer patients. Studies also have linked altered mitochondrial metabolism to changes in immune cell activation in TIME. Recent publications revealed a novel immunomodulatory role for triphenylphosphonium-based mitochondrial-targeted drugs (MTDs). These are synthetically modified, naturally occurring molecules (e.g., honokiol, magnolol, metformin) or FDA-approved small molecule drugs (e.g., atovaquone, hydroxyurea). Modifications involve conjugating the parent molecule via an alkyl linker chain to a triphenylphosphonium moiety. These modified molecules (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, Mito-hydroxyurea) accumulate in tumor cell mitochondria more effectively than in normal cells and inhibit mitochondrial respiration, induce reactive oxygen species, activate AMPK and redox transcription factors, and inhibit cancer cell proliferation. Besides these intrinsic effects of MTDs in redox signaling and proliferation in tumors, MTDs induced extrinsic effects in the TIME of mouse xenografts. MTD treatment inhibited tumor-suppressive immune cells, myeloid-derived suppressor cells, and regulatory T cells, and activated T cells and antitumor immune effects. One key biological disparity in Black cancer patients was related to altered mitochondrial oxidative metabolism; MTDs targeting vulnerabilities in tumor cells and the TIME may help us understand this biological disparity. Clinical trials should

Abbreviations: ERR-1, estrogen-related receptor 1; FeS, iron-sulfur; M1, tumor inhibitory; M2, tumor promoting; MDSC, myeloid-derived suppressor cell; Mito, mitochondria; MTD, mitochondria-targeted drug; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death protein 1; PD-L1, programmed death receptor ligand 1; PET-CT, positron emission tomography–computed tomography; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TIL, tumor-associated lymphocytes; TIME, tumor immune microenvironment; TPP^+, triphenylphosphonium cation; T_{regs}, regulatory T cells.

include an appropriate number of Black and Hispanic cancer patients and should validate the intratumoral, antihypoxic effects of MTDs with imaging.

KEYWORDS
mitochondrial drugs, OXPHOS inhibitors, racial disparity, tumor microenvironment

1 | INTRODUCTION

Most cancer patients do not respond positively to immunotherapy. Strategic development of additional combinatorial drug regimens is necessary. Tumor cells evade the immune system through upregulation of programmed death receptor ligand 1 (PD-L1) expression that binds to programmed cell death protein 1 (PD-1) in T cells, resulting in immunosuppression. One way to prevent cancer cells from immune evasion is to decrease the expression of PD-L1 or hinder the binding of PD-L1 to PD-1.[1,2] Therefore, a major challenge is to target-specific metabolic pathways in cancer cells without adversely impairing immune cells while enhancing antitumor immunity. Tumor cell metabolism is primarily governed by the Warburg effect or aerobic glycolysis. However, glucose metabolism is essential not only for cancer cells but also for T cells and macrophages. Thus, targeting cancer cells alone using 2-deoxy-d-glucose and other glycolytic inhibitors will also adversely affect immune cells. Targeting oxidative phosphorylation (OXPHOS), in particular, mitochondrial complex I of the mitochondrial electron transport chain, is emerging as a potent and selective antiproliferative strategy in tumor cells.[3–12] Hypoxic tumors with a reduced capacity for compensatory glycolysis are more susceptible to OXPHOS inhibitors.[12] Modulators of glutamine metabolism in the Krebs cycle are being developed in cancer therapy.[13]

Mitochondrial OXPHOS inhibitors also target cancer-associated immune cells in the tumor immune microenvironment (TIME)[10] and play an important role in cancer immune evasion.[14] Inhibition of the OXPHOS function in cancer cells and the concomitant decrease in tumor hypoxia-induced remodeling of the TIME and the antitumor response.[8] Recent reports suggest that triphenylphosphonium (TPP^+)-containing mitochondrial drugs inhibit tumor-suppressive cells, such as the myeloid-derived suppressor cells (MDSCs) and regulatory T cells (T_{regs}), in the TIME.[15,16] MDSCs suppress T cells that destroy tumor cells.[17] Targeting MDSCs and T_{regs} is emerging as an antitumor therapeutic strategy.[18] Current chemotherapeutics (e.g., gemcitabine and 5-fluorouracil) used to inhibit MDSCs cause bone marrow suppression; therefore, less toxic and more targeted agents are needed to suppress MDSCs and/or suppressive neutrophils and enhance the cytotoxic antitumor function of T cells.[19–21] Investigating the immunomodulatory effects of mitochondria-targeted drugs (MTDs), especially TPP^+-based drugs, is an area of intense research.[16,22] Emerging research indicates that the TIME in Black cancer patients consists of more protumorigenic and immunosuppressive factors than in white cancer patients.[23,24] Developing potent yet nontoxic MTDs may help overcome this biological disparity.

2 | MTDs CONJUGATED TO TPP^+, OXPHOS INHIBITION, AND REDOX SIGNALING

The most studied and widely used mitochondria-targeting vector is TPP^+.[3,25–28] TPP^+ possesses a single positive charge that is delocalized over three phenyl groups, stabilizing resonance. In addition to the charge, the hydrophobicity of the lipophilic cation favors the interaction with the hydrophobic inner mitochondrial membrane. Driven by the membrane potential, the concentration of the TPP^+ in the cytoplasm increases by about 5–10-fold, compared with that of the extracellular space. The resulting accumulation of TPP^+ in the cytoplasm is about 100–500 times that in the extracellular space (Figure 1). This provides a highly targeted and effective mitochondrial vector. The advantages of TPP^+-based targeting molecules are the stability of TPP^+ in the biological system, the low chemical reactivity toward cellular components, the combination of lipophilic and hydrophilic moieties, and the ease of synthesizing large quantities of molecules for in vivo work.[28]

TPP^+-based MTDs conjugated to natural products or FDA-approved drugs are potent, tumor-selective, and relatively nontoxic (with minimal off-target pharmacology) in cells and preclinical tumor xenografts.[3–10,15,16] Several natural products (e.g., honokiol, magnolol, metformin) and FDA-approved drugs (e.g., atovaquone, hydroxyurea) conjugated to the TPP^+ moiety (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, Mito-hydroxyurea) (Figure 1) exhibit significantly more antiproliferative potency than other non-TPP^+ mitochondrial inhibitors (e.g., metformin, phenformin, atovaquone, IACS-010759) in different cancer cells.

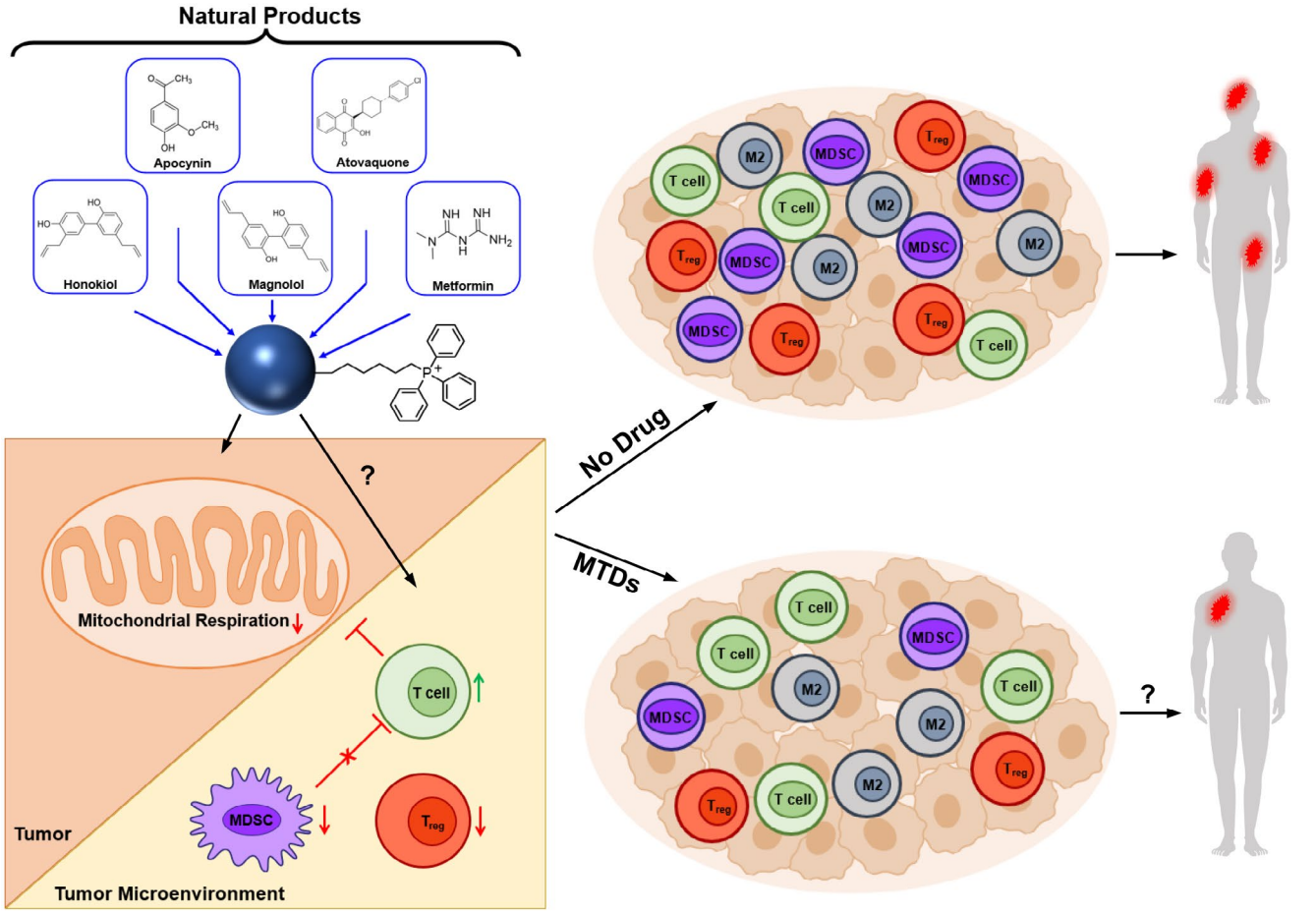

FIGURE 1 A hypothetical picture showing how MTDs could potentially change the immunosuppressive microenvironment to an antitumor microenvironment and cause a decrease in breast tumor metastasis. M2, tumor promoting; MDSCs, myeloid-derived suppressor cells; MTDs, mitochondria-targeted drugs; T_{reg}, regulatory T cells. A portion of this figure was Reprinted from iScience, 24, Cheng G, Hardy M, Topchyan P, Zander R, Volberding P, Cui W, Kalyanaraman B., Mitochondria-targeted hydroxyurea inhibits OXPHOS and induces antiproliferative and immunomodulatory effects, Pages No. 102673, ©2021, with permission from Elsevier; a portion of this figure was reprinted with permission from Zielonka et al.[28] ©2017 American Chemical Society; and a portion of the figure is licensed under CC BY, copyright ©2020 Kim G, Pastoriza JM, Condeelis JS, Sparano JA, Filippou PS, Karagiannis GS, Oktay MH. The contribution of race to breast tumor microenvironment composition and disease progression. Front Oncol. 2020 Jun 30;10:1022. 10.3389/fonc.2020.01022

3 | MITO-HONOKIOL INHIBITS LUNG CANCER METASTASIS TO THE BRAIN

Previously, using low-temperature electron paramagnetic resonance, we determined the mitochondrial redox changes in pancreatic cancer cells treated with TPP^+-containing mitochondria-targeted agents.[29] Based on the electron paramagnetic resonance spectral changes of mitochondrial complex I iron-sulfur (FeS) clusters, $[2Fe2S]^+$ and $[4Fe\text{-}4S]^+$, we surmised that TPP^+-containing MTDs (mitochondrial complex I inhibitors) bind closer to the NADH-dehydrogenase site in the mitochondrial complex I dictated by the NAD^+/NADH couple.[30] Mito-honokiol is synthesized by conjugating TPP^+ through an alkyl side chain to honokiol, a component of magnolia tree bark extract and a widely used nutritional supplement. Mito-honokiol inhibits mitochondrial complex I-induced oxygen consumption, induces superoxide and hydrogen peroxide formation and activation of AMPK, inhibits signal transducer and activator of transcription 3 (STAT3) phosphorylation, and inhibits proliferation of cancer cells.[9] Further, Mito-honokiol inhibits lung cancer progression and prevents metastasis of lung cancer cells to lymph nodes and to the brain.[9] From a mechanistic standpoint, the antitumor and antimetastatic effects were shown to be mediated by the STAT3 pathway. Knockdown of STAT3 abrogated both the antiproliferative and antimetastatic effects of Mito-honokiol.[9] Mito-honokiol inhibits STAT3 phosphorylation irrespective of the epidermal growth factor receptor mutation status in lung cancer cells.[9] Reports indicate that a decrease in the core body temperature and death result from the excessive inhibition of OXPHOS.[12] Mito-honokiol did not elicit

these effects.[9] Currently, treatment of lung cancer metastasis does not start until after diagnosis of brain cancer. Mito-honokiol treatment inhibits metastasis of primary cancer to brain. Emerging research is focused on metabolic reprogramming of metastatic lung cancer cells and their vulnerability to MTDs.[7–10,31]

4 | ANTIPROLIFERATIVE EFFECTS OF MITO-MAGNOLOL IN DRUG-RESISTANT MELANOMA CELLS

Drug resistance to kinase inhibitors is attributed to metabolic reprogramming from glycolysis to mitochondrial oxidative metabolism. Bioenergetic mapping results showed that tumor cells with enhanced mitochondrial OXPHOS were more sensitive to TPP^+-based MTDs and other OXPHOS inhibitors.[32] There are currently no effective drugs for treating melanoma, an aggressive form of skin cancer. B-Raf serine/threonine kinase, or BRAF, inhibitor antiglycolytic drugs induce a rapid onset of drug resistance. BRAF inhibitors cause metabolic reprogramming from a glycolytic phenotype to an OXPHOS phenotype that is attributed to resistance against antiglycolytic kinase inhibiting drugs (e.g., vemurafenib). The increased dependence on OXPHOS for energy makes OXPHOS a vulnerable target in drug-resistant melanoma cells. Increased mitochondrial biogenesis and upregulated OXPHOS genes are associated with enhanced mitochondrial respiration in drug-resistant melanoma cells. A mitochondria-targeted analog of magnolol (Mito-magnolol) was shown to potently inhibit melanoma cell proliferation and tumor growth in murine melanoma xenografts.[22,33] Mito-magnolol is synthesized by conjugating a TPP^+ moiety via an alkyl side chain to magnolol.[33] Magnolol is present in abundance in magnolia extract, a traditional herbal medicine used effectively for centuries in East Asia to treat inflammatory diseases. Mito-magnolol belongs to a new class of mitochondria-targeted polyphenolic drugs.

Mito-magnolol potently inhibits mitochondrial complex I-induced mitochondrial respiration, blocks cell cycle progression, and inhibits proliferation of melanoma cells, primarily through the downregulation of mTOR/AKT signaling and mitophagy.[33]

Mito-magnolol induced AMPK–threonine 172 phosphorylation, activating AMPK signaling, mitophagy, and energy-related proteins in melanoma cells. Mito-magnolol treatment was equally effective in inhibiting drug-resistant melanoma cells (with enhanced OXPHOS).[33]

Mito-magnolol inhibited tumor progression in an immune-competent mouse xenograft model.[22] Also, Mito-magnolol remodeled the TIME in a mouse melanoma model. Mito-magnolol induced infiltration of T cells, decreased MDSCs, and decreased tumor-associated macrophages in melanoma tumors.[22] The antitumor effect of Mito-magnolol is inhibited by immune depletion.[22] The antitumor immunity effect of mitochondria-targeted polyphenolics is an exciting area of therapeutic drug targeting and TIME remodeling.

5 | ANTITUMOR IMMUNE EFFECTS OF MITO-ATOVAQUONE

Recent reports indicate that selective targeting and inhibiting of mitochondrial complex III mitigate and reverse immunosuppression by T_{regs}, promoting the function of effector T cells.[34] T_{regs} suppress the antitumor immunity that greatly hampers immunotherapy. Inhibitors of mitochondrial complex III (e.g., antimycin A) and not complex I (e.g., rotenone) reversed the immunosuppressive function of T_{regs}.[34] Although several relatively nontoxic mitochondrial complex I inhibitors exist (excluding rotenone which is toxic), the availability of mitochondrial complex III inhibitors is relatively scarce except for antimycin A and atovaquone. $Mito_{10}$-atovaquone is synthesized by conjugating TPP^+ via an alkyl side chain to atovaquone, an FDA-approved antimalarial drug.[15] $Mito_{10}$-atovaquone inhibits both mitochondrial complex III- and complex I-induced oxygen consumption.[15] We showed, for the first time, that conjugating atovaquone to TPP^+ and increasing the aliphatic linker side chain length generates Mito-atovaquone analogs (e.g., $Mito_4$-atovaquone and $Mito_{10}$-atovaquone) that are potent inhibitors of mitochondrial complex I- and complex III-induced oxygen consumption in cancer cells.[15] $Mito_4$-atovaquone and $Mito_{10}$-atovaquone effectively inhibit T_{reg} differentiation and survival while stimulating effector T cell response. These compounds represent a new class of antitumor and immunoregulatory drugs. The TIME is a potentially vulnerable target in cancer therapy. MTDs (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, Mito-hydroxyurea) inhibit immunosuppressive cells (e.g., MDSCs and T_{regs}) and increase the infiltration of cytolytic T cells in the TIME as well as Mito-magnolol and T_{regs}.[15,16,33]

6 | OXPHOS INHIBITORS, MDSCs, AND METASTATIC CANCER

The metabolic reprogramming (enhanced OXPHOS) that occurs in metastatic cancer cells likely plays a major role in metastatic cancer cell survival and progression.[31,35] Reports indicate that an OXPHOS inhibitor, IACS-010759,

inhibits melanoma brain metastasis.[10] The mitochondrial complex I inhibitor also inhibits MDSCs in the metastatic TIME. TPP^+-conjugated OXPHOS inhibitors of mitochondrial complex I and complex III—Mito-magnolol, Mito-atovaquone, and Mito-hydroxyurea—are potentially suitable antimetastatic drugs.[15,33] It was reported that brain metastases from patients with melanoma displayed a considerable degree of immunosuppression and increased expression of genes related to OXPHOS. IACS-010759, a reported mitochondrial complex I inhibitor, blocked metastasis formation in mouse models.[10] Mito-atovaquone and Mito-lonidamine are potent OXPHOS inhibitors and inhibit lung cancer metastasis to the brain in mouse models.[15,36]

7 | OXIDATIVE METABOLISM, A BARRIER TO IMMUNOTHERAPY

Hypoxia (a lack of oxygen) is a key hallmark of tumors and the TIME. Hypoxia is associated with a decreased metabolic function of T cells in the TIME and inhibits antitumor immunity. Studies showed that tumors with enhanced oxidative metabolism (due to metabolic reprogramming) responded poorly to immunotherapy (PD-1 blockade). Tumors with decreased mitochondrial respiration and oxidative metabolism responded more positively to immunotherapy.[37–39] This was attributed to enhanced T cell exhaustion in the TIME of tumors with enhanced oxidative metabolism (increased hypoxia in the TIME) in contrast to tumors with less mitochondrial oxidative metabolism (decreased hypoxia in the TIME). These findings suggest that it may be possible to manipulate tumor hypoxia and remodel the TIME using MTDs.

Emerging research suggests that targeted therapy to remodel the TIME and enhance T cell function would increase the antitumor effect and improve the efficacy of immunotherapeutic effects of cancer.[40–42] Remodeling processes enhancing the oxygen tension of the TIME was proposed as a viable therapy.[43] Higher metabolic rates in tumors result in tumor hypoxia, especially in solid tumors with disorganized vasculature.[44,45] One approach to decrease tumor hypoxia (i.e., to enhance oxygen concentration in tumors) is to decrease tumor oxygen consumption.[11] Decreased hypoxia in tumors is a pharmacodynamic response of MTDs that can be quantitated by positron emission tomography imaging.[46,47] Immunotherapeutic efficacy was potentiated by a metformin-induced decrease in tumor hypoxia.[48] Previously, we showed that inhibition of OXPHOS by Mito-metformin enhances radiation-induced pancreatic cancer cell killing, which is attributable to increased oxygen tension or decreased hypoxia in pancreatic cancer cells.[4]

8 | MTDs AND CHECKPOINT INHIBITORS

Tumor hypoxia facilitates the recruitment of immunosuppressive cells (MDSCs, T_{regs}, tumor-associated macrophages) to the TIME.[49] In addition, immunosuppressive metabolites and cytokines are released by both tumor cells and immune cells under hypoxia. Immune checkpoint molecules (e.g., PD-L1, cytotoxic T-lymphocyte-associated protein 4) are also upregulated. All of these adaptations to tumor hypoxia blunt an effective immune response. Restoring the oxygen supply to tumors was shown to reactivate the antitumor response because of decreased immunosuppressive cells and increased effector cytotoxic T cells in the TIME.[50,51] In a paradoxical study, oxygen was shown to impair the anticancer activity of T cells in mice, and inhibiting the oxygen-sensing capability of immune cells prevented lung metastasis.[52] Recent studies show that radiotherapy combined with inhibition of OXPHOS is an effective strategy to overcome the barrier to PD-1 immunotherapy.[53,54] The combination of IACS-010759, a mitochondrial complex I inhibitor, with radiotherapy proved to be a promising strategy to treat PD-1-resistant lung cancer. Several clinical trials are underway investigating the antihypoxic effects of FDA-approved drugs for other diseases (e.g., metformin, atovaquone, papaverine) in combination with radio and immunotherapies of cancer. Metformin, a weak inhibitor of mitochondrial complex I, was more effective in treating Black cancer patients.[55,56] Metformin was shown to decrease PD-L1 expression through activating the Hippo signaling pathway in colorectal cancer cells.[57] A clinical trial investigating the use of metformin to reduce disparities in breast cancer is ongoing.[58] Mito-metformin containing longer aliphatic side chains that are significantly more potent than metformin in inhibiting pancreatic cancer cell proliferation and growth may be a viable candidate drug for future clinical trials designed to decrease racial disparities in breast cancer.

9 | OXPHOS INHIBITION, AMPK ACTIVATION, AND ENHANCED IMMUNOSUPPRESSIVE TIME

AMPK, a master regulator of cellular energy homeostasis, is typically activated by increased intracellular AMP.[59,60] We previously showed that OXPHOS inhibitors stimulate a signaling pathway for antiproliferative effects, linking mitochondrial complex I inhibition to AMPK activation[4,6,9,33,36] and leading to inhibition of STAT3 ser727 phosphorylation.[61] AMPK activation inhibits the functions of MDSCs.[62–65] The MTD, phenformin,

inhibits MDSCs and enhances the antitumor activity.[66] Cumulative evidence suggests that STAT3 activation leads to immunosuppression, and inhibiting STAT3 signaling is an effective strategy to improve antitumor immunity.[67,68] Mitochondria-targeted polyphenolics (e.g., Mito-honokiol, Mito-magnolol) and Mito-metformin activate AMPK phosphorylation in multiple cancer cells and inhibit immunosuppressive cells in the TIME.

10 | MITOCHONDRIAL BIOMARKERS AND PERSONALIZED THERAPY

Developing novel therapeutic strategies targeting mitochondria might decrease or prevent racial health disparities.[69,70] Mitochondrial determinants of cancer health and the mitochondrial basis of cancer disparities are unknown.[70] However, recent reports suggest that mitochondrial biomarkers could predict tumor progression and outcome.[71,72] Atovaquone decreased tumor hypoxia or increased tumor oxygenation and inhibited hypoxia-regulated gene expression in lung cancer patients.[73] In hypoxia PET-CT (positron emission tomography–computed tomography), a key pharmacodynamics endpoint was the reduction in hypoxia-regulated genes, which were down-regulated in atovaquone treatment of non-small-cell lung cancer patients.[73] OXPHOS targeting is an effective way to inhibit hypoxic cancer cells. Hypoxic monitoring may, therefore, serve as an effective biomarker in therapeutic selection and treatment.

11 | MITOCHONDRIAL DYSFUNCTION AND RACIAL DISPARITIES

Increasing evidence supports the existence of racial and ethnic disparities in the breast cancer immune microenvironment.[23] Higher levels of pro-tumorigenic factors (e.g., macrophages, T_{regs}, exhausted T cells) were identified in the TIME of Black breast cancer patients as compared with white counterparts.[23,24,74] Upregulation of genes associated with OXPHOS was identified in tumor samples obtained from Black cancer patients.[75] Tumors from Black cancer patients have more mitochondria, ERR-1 (estrogen-related receptor 1), and peroxisome PGC-1α (proliferator-activated receptor gamma coactivator 1-alpha).[76] Clinical trial data show that Black cancer patients respond better to mitochondrial inhibitors (e.g., metformin) than white cancer patients.[55] Developing the next generation of mitochondrial inhibitors was perceived to be a promising therapeutic strategy to mitigate or prevent enhanced mortality in Black cancer patients.[75] A newly developed mitochondria-targeted atovaquone (i.e., $Mito_{10}$-ATO) inhibits MDSCs and T_{regs}.[15] It is conceivable that newly developed, mitochondria-targeted modified natural products and FDA-approved drugs (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, and Mito-hydroxyurea) and their analogs potentially could be useful in understanding the biological racial disparity in cancer mortality. Additional research centered on understanding the role of mutations in the epidermal growth factor receptor, epidermal growth factor receptor tyrosine kinase inhibitors, the OXPHOS pathway,[77] and racial disparity in cancer patients is needed.

A recent report highlights that changes in mitochondria (enrichment of OXPHOS in tumors from Black patients) could be a biomarker and provides a rationale for the repurposing of mitochondrial inhibitors to treat cancers in Black patients.[76] Hypoxic gene expression signatures using RNA sequencing may be used as a biomarker for patient selection and treatment with MTDs.[73] A recent report suggests a biomarker-based approach to patient selection to overcome or mitigate racial disparities in clinical cancer trials.[78]

12 | UNANSWERED QUESTIONS

How mitochondrial inhibition of tumor tissues decreases immunosuppression in the TIME is not known. Whether this effect is tumor intrinsic, tumor extrinsic, or both remains to be determined. Dynamic variations in the mitochondrial membrane potentials of immune cells (i.e., T cells, T_{regs}, natural killer cells, macrophages) that determine the toxicity of MTDs are not known. The effect of MTDs on PD-L1 and other checkpoint protein expression in cancer cells needs to be examined in detail.

How MTD-mediated inhibition of complex I-induced mitochondrial respiration affects antigen presentation on major histocompatibility class 1 molecules, including tumor peptides, needs to be investigated in detail. Studies suggest a compelling role for mitochondria in antigen processing and presentation[79,80] as well as in cancer immune evasion.[81] Important considerations include strategies to counteract the inactivation of the major histocompatibility class 1 pathway, and how MTD-induced inhibition of respiration affects cytokine (e.g., interferon gamma) response in antigen-presenting cells.[82,83]

How epigenetic modifications (DNA methylations, histone modifications, mRNA expression modulation) that affect changes in the gene expression (not caused by changes in the DNA sequences) are influenced by MTD-mediated repression of mitochondrial respiration in cancer cells is not known. Epigenetic modifications have

been used as predictive biomarkers in cancer.[84] The importance of epigenetic events in racial disparity is increasingly recognized.[85–88] One of the primary characteristics of cancer cells is altered metabolism (i.e., the Warburg effect). Inhibitors of glycolytic metabolism in tumors affect epigenetic modifications.[89] Understanding the interplay between alterations in DNA methylations, histone modifications, chromatin remodeling in light of altered tumor metabolism, and metabolic reprogramming is critical to understanding the implications of mitochondrial dysfunction and racial disparity in cancer treatment.[90]

Mitochondrial reactive oxygen species (ROS) and their significance in MTD-dependent antiproliferative and antitumor effects are not known. N-acetylcysteine, a membrane-permeable cysteine precursor, is used as an ROS scavenger and a potent antioxidant. Its cytoprotective effect and/or inhibition of oxidation of fluorescent dye were related to its ability to scavenge ROS (superoxide or hydrogen peroxide) and modulate redox signaling effects in cancer cells treated with TPP^+-containing agents.[91] However, neither superoxide nor hydrogen peroxide reacts at an appreciable rate with N-acetylcysteine. This calls into question the ROS scavenging as an antioxidant mechanism of N-acetylcysteine. N-acetylcysteine can enhance intracellular glutathione and glutathione-dependent hydroperoxide-removing antioxidant enzyme machinery. Thus, the proposed antioxidant mechanism of N-acetylcysteine is not related to the direct scavenging of ROS.

Although most of the previous preclinical work with OXPHOS inhibitors was performed in immunodeficient mice, the involvement of both tumor mitochondria and the TIME in the antitumor mechanism of MTDs was demonstrated in immune-competent mice.[22] Mitochondrial transfer from the stromal cells in the TIME to tumor cells was shown to occur in several cancers, including acute myeloid leukemia.[92,93] However, the mechanism of transfer needs to be determined. Although an ROS mechanism has been proposed, the identity of the species responsible for the transfer has not been determined. Rigorous characterization of diagnostic marker products of fluorescent dyes, as previously described,[30] need to be determined.

13 | CONCLUSIONS AND FUTURE PERSPECTIVES

The TIME in Black cancer patients consists of more protumorigenic factors and mitochondrial dysfunction than in white cancer patients. Thus, developing a highly potent, less toxic, and tumor/TIME selective next generation of mitochondrial OXPHOS inhibitors is timely and critical in overcoming racial and ethnic disparities in cancer treatment. Poor accrual of Black and Hispanic cancer patients in clinical trials has hindered our understanding of the biological basis of racial disparity. Clinical trials should include Black and Hispanic cancer patients and combinatorial treatments (potent OXPHOS inhibitors alleviating hypoxia and radiation, immunotherapy). Patient selection should be based on imaging studies that validate hypoxic modification of drugs in Black and Hispanic cancer patients.

It is conceivable that newly developed, mitochondria-targeted modified natural products and FDA-approved drugs (e.g., Mito-honokiol, Mito-magnolol, Mito-metformin, Mito-atovaquone, Mito-hydroxyurea), as well as those developed in other labs,[94,95] potentially could be useful in understanding the biological racial disparity in cancer mortality.

Recently, mono-alkyl lipophilic cations (also referred to as cationic surfactants) consisting of a dimethyl sulfonium cation and a long alkyl side chain were reported to inhibit mitochondrial respiration of fungi and exert a strong antifungal mechanism.[13,96] To establish the generality of the OXPHOS inhibition mechanism, additional cationic molecules should be tested.

Do all complex I inhibitors have the potential to become anticancer agents? The lack of effect of complex I inhibitors on normal cells must be studied in all cases.

MTDs combined with standard-of-care chemotherapy, radiation therapy, and immunotherapy are likely to have potentiating effects. Ongoing research in preclinical models suggests that MTDs augment the efficacy of PD-L1 inhibitors. These combinational modalities may counteract the immunosuppressive TIME and enhance immunotherapy using the checkpoint inhibitors.[97]

Emerging research reports nanotube-mediated transfer of mitochondria from T cells to cancer cells as an immune evasion mechanism,[98] further substantiating the urgent need to develop more potent MTDs. Future research should also focus on the effect of MTDs on nanotube or nanotube assembly machinery formation. Previous research has demonstrated that dual targeting of mitochondria with MTDs and antiglycolytics (e.g., 2-deoxy-d-glucose) significantly inhibits the generation of adenosine triphosphate in breast cancer cells.[27] This combinatorial therapeutic approach may hinder nanotube-mediated mitochondrial trafficking between immune cells and cancer cells.

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B.K. is an inventor of US Patent No. 10,836,782 (issued November 17, 2020)/European Patent No. 3307254 (issued August 5, 2020), "Mito-honokiol compounds and methods of synthesis and use thereof;" S Patent No. 11,083,739 (issued August 10, 2021), "Mito-magnolol compounds and methods of synthesis and use thereof;" US Patent No. 9,956,233 (issued May 1, 2018), "Neuroprotection by mitochondria-targeted metformin."

AUTHOR CONTRIBUTIONS

Balaraman Kalyanaraman wrote the paper.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ORCID

Balaraman Kalyanaraman https://orcid.org/0000-0002-9180-8296

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