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The role of mitochondria in the resistance of melanoma to PD-1 inhibitors

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Abstract

Malignant melanoma is one of the most common tumours and has the highest mortality rate of all types of skin cancers worldwide. Traditional and novel therapeutic approaches, including surgery, targeted therapy and immunotherapy, have shown good efficacy in the treatment of melanoma. At present, the mainstay of treatment for melanoma is immunotherapy combined with other treatment strategies. However, immune checkpoint inhibitors, such as PD-1 inhibitors, are not particularly effective in the clinical treatment of patients with melanoma. Changes in mitochondrial function may affect the development of melanoma and the efficacy of PD-1 inhibitors. To elucidate the role of mitochondria in the resistance of melanoma to PD-1 inhibitors, this review comprehensively summarises the role of mitochondria in the occurrence and development of melanoma, targets related to the function of mitochondria in melanoma cells and changes in mitochondrial function in different cells in melanoma resistant to PD-1 inhibitors. This review may help to develop therapeutic strategies for improving the clinical response rate of PD-1 inhibitors and prolonging the survival of patients by activating mitochondrial function in tumour and T cells.

Keywords Mitochondria, Melanoma, PD-1 inhibitor, Drug resistance, Combined therapy

Introduction

Melanoma, which is usually referred to as malignant melanoma, is a type of skin cancer that develops from melanocytes. It mostly occurs in the skin, mucous membranes and viscera. Although melanoma accounts for only 7% of total cases of skin cancer, almost 90% of patients die, accounting for 65% of all skin cancer-related deaths [1–3]. Some studies have shown that long-term skin exposure to ultraviolet (UV) light greatly increases the incidence of melanoma and is one of the main factors inducing melanoma [2]. According to statistics, differences in sex and age also affect the incidence of melanoma. The incidence of cutaneous melanoma is higher among men than among women worldwide. For example, in 2020, there were about 325,000 new cases of melanoma (174,000 males and 151,000 females) and 57,000 deaths (32,000 males and 25,000 females) worldwide [4, 5]. Moreover, approximately 40% of patients with malignant melanoma are aged > 65 years, who not only present with more aggressive clinicopathological features but are often diagnosed with advanced cancer [6].

Melanoma is generally classified according to the tumour, node, and metastasis (TNM) staging system: stages I–II, patients with local disease; stage III, lymph node-positive disease; stage IV, advanced/metastatic disease [7]. The key to evaluating the severity of melanoma

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is the assessment of clinicopathological features such as tumour thickness (Breslow depth), physiological and pathological status of the lymphoid system and ulcers and tumour cell metastasis. The treatment of melanoma varies with the disease stage. In melanoma stages I–II, after the cancer site is determined based on clinical manifestations, surgical resection and adjuvant systemic treatment are used to reduce the risk of recurrence postoperatively [8, 9]. However, patients with lymph node-positive disease or tumour metastasis are not eligible for surgical treatment and may require targeted therapy, immunotherapy or combination therapy for effective treatment [10–13].

Programmed death-1 (PD-1) and its ligand (PD-L1) are co-inhibitory protein receptors expressed on the surface of lymphocytes. Their main physiological functions are maintaining self-tolerance and limiting inflammation in normal tissues [12]. Monoclonal antibodies against PD-1 have demonstrated efficacy in the clinical treatment of melanoma, non-small cell lung cancer and renal cell carcinoma [14] and are one of the most important treatment agents for melanoma [15]. However, anti-PD-1 therapy does not effectively block tumour activity in all patients. Although some patients exhibit a clinical response, a large proportion of these patients may develop acquired resistance after the initial reaction [16].

Mitochondria are key cytoplasmic organelles, which are the main site for aerobic respiration. Some studies have shown that healthy mitochondria can not only inhibit melanoma metastasis but also increase survival. Additionally, activating mitochondrial function can increase the anti-tumour activity of $CD8^+$ T cells [17–19].

Based on the relationship among melanoma, PD-1 inhibitors and mitochondria, this review discusses the recent research progress on the role of mitochondria in the treatment of melanoma resistance to PD-1 inhibitors to explore strategies for improving the survival rate of patients through the combination of mitochondrial activation and PD-1 inhibition.

Resistance mechanism of PD-1 inhibitors in melanoma

Immune checkpoint inhibitor-based therapy is the most effective treatment for metastatic melanoma [20]. To date, three immune checkpoint inhibitors have been approved for the treatment of melanoma: the anti-PD-1 antibodies nivolumab and pembrolizumab and the anti-CTLA-4 antibody ipilimumab [21]. In recent years, PD-1 and PD-L1 inhibitors have been the major focus of research on the immunotherapy of melanoma (Table 1) [22, 23].

PD-1, also known as CD279, is usually expressed on activated T, B and natural killer cells and is highly expressed on tumour-specific T cells [12, 38, 39]. Immune cells expressing PD-1 identify cells as normal by recognising the PD-1 ligand (PD-L1/2) released by the cells, which can suppress the immune system [40]. PD-1 regulates the immune system by inducing apoptosis of mature T cells [41, 42]. In addition, PD-1 can reduce the apoptosis of regulatory T cells, thus limiting the inflammatory response in normal tissues (regulatory T cells are anti-inflammatory cells that inhibit immune responses to self-antigens) [43]. These functions of PD-1 can reduce tissue damage during pathological disturbances such as infection. However, in the tumor microenvironment (TME) of melanoma, after identifying an abnormal antigen in major histocompatibility complex (MHC), T cells release interferon-gamma (IFN-γ) to improve tumour-killing efficiency. IFN-γ released by $CD8^+$ T cells can upregulate the expression of PD-L1 on tumour and stromal cells [44]. Simultaneously, T-cell receptor signalling

Table 1 The current status of immunotherapy for melanoma

Therapeutic method	Reagent	Mechanism	References
CTLA-4inhibitor	Ipilimumab	Anti-CTLA4 antibody	[24, 25]
	Tremelimumab	Anti-CTLA4 antibody	[26]
PD-1 inhibitor	Nivolumab	Anti-PD-1 antibody	[27]
	Pembrolizumab	Anti-PD-1 antibody	[15, 28]
	Cemiplimab	Anti-PD-1 antibody	[29]
PD-L1 inhibitor	Atezolizumab	Anti- PD-L antibody	[30, 31]
	Avelumab	Anti- PD-L antibody	[32]
	Durvalumab	Anti- PD-L antibody	[33]
Others	Interferon-alfa2b and pegylated-interferon-alpha2b	Cytokine activation of T-Cells	[34, 35]
	Talimogene laherparepvec(T-VEC)	Oncolytic virus	[36]
	Relatlimab	Anti- LAG-3 antibody	[37]

can upregulate the expression of PD-1 on T cells, and the interaction between PD-1 and PD-L1 can lead to misidentification of tumour cells by T cells, thus playing a negative role in the anti-tumour effect [45, 46]. Studies have shown that the regulatory effects of melanoma cells on immune checkpoints can be overcome by using antibodies against PD-1 and PD-L1/2 [14, 47, 48]. In particular, PD-1 inhibitors (nivolumab and pembrolizumab) can effectively block the interaction between PD-1 and its ligands PD-L1 and PD-L2, thus allowing the occurrence of immune responses [28, 49–51]. In addition, studies have shown that the abundance of circulatory PD-1$^+$ Tregs (Regulatory T cells) is rapidly decreased, the development of melanoma is significantly inhibited and the risk of metastasis is significantly reduced after anti-PD-1 therapy [52].

However, most patients cannot benefit from anti-PD-1 therapy, and a large number of patients who respond to anti-PD-1 therapy develop acquired resistance after the initial response in clinical settings [16]. Insufficient tumour immunogenicity, dysfunction of MHC, presence of other inhibitory receptors, IFN-γ signal resistance and an immunosuppressive microenvironment play a key role in the development of resistance to anti-PD-1/PD-L1 therapy (Fig. 1) [16].

Insufficient immunogenicity of melanoma

The anti-tumour effects of PD-1 blockade depend on the presence of antigen-specific T-cell responses in the tumour microenvironment. They require antigen-presenting cells (APCs) to present potential tumour antigens to activate CD8$^+$ T cells and trigger subsequent anti-tumour activity [53]. In a study, patients with melanoma were treated with anti-PD-1 therapy, and the tissue samples of responders and non-responders were subsequently compared. The results showed that patients who were sensitive to anti-PD-1 therapy contained more non-synonymous single nucleotide variants (SNVs) and

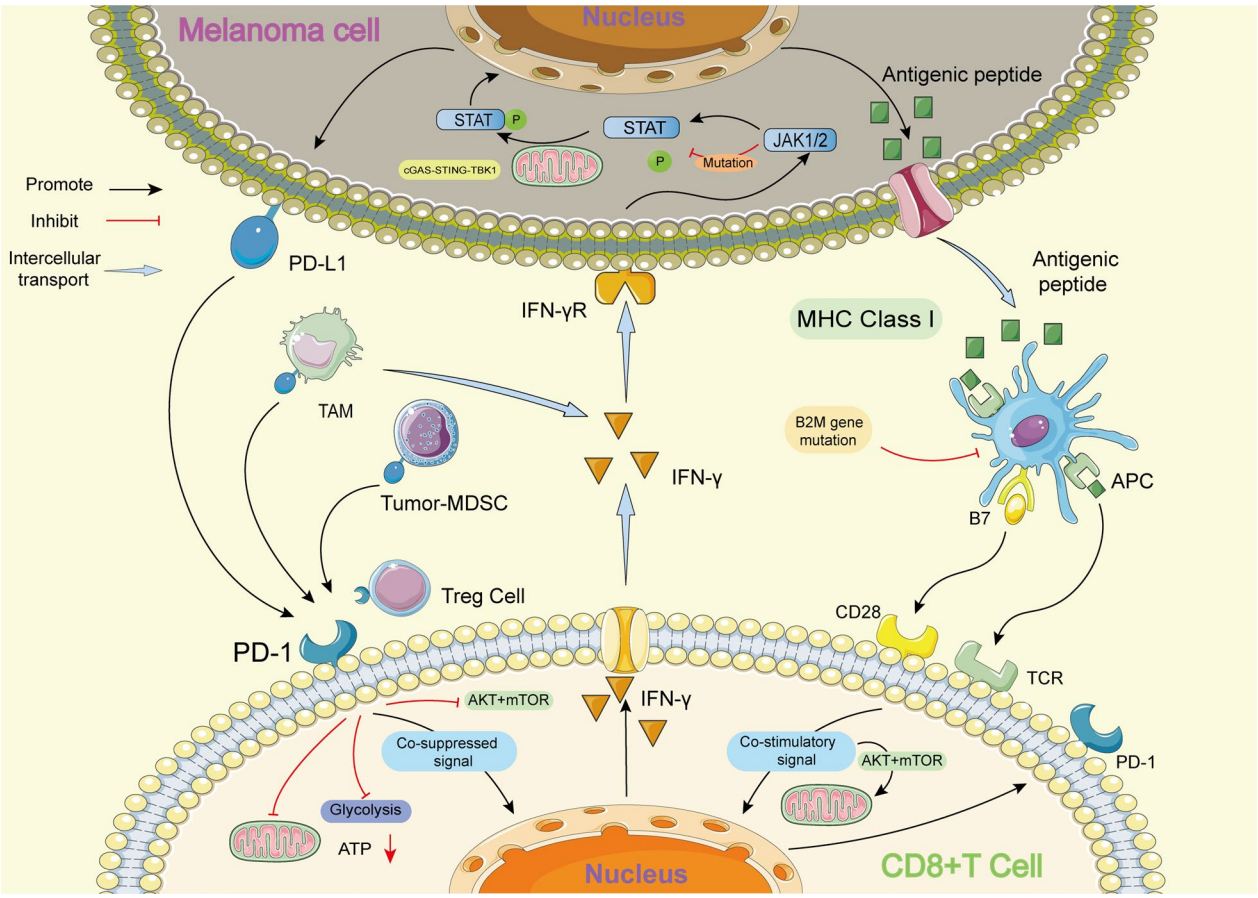

Fig. 1 Mechanism of melanoma resistance to PD-1 inhibitors. The main mechanisms of melanoma resistance to PD-1 inhibitors include: (1) Insufficient immunogenicity of tumor; (2) MHC dysfunction caused by B2M mutation; (3) CD8$^+$T cells transformed into depleted T cells (Tex) due to continuous stimulation of tumor antigen; (4) IFN- γ signal plays an immunosuppressive role; (5) interference from other cells in tumor microenvironment. MHC: Major histocompatibility complex; B2M: β 2-microglobulin; APC: Antigen-presenting cells; STAT: Signal transducer and activator of transcription; JAK: Janus Kinase; TAM: Tumor-associated macrophages; MDSC: Myeloid-derived suppressor cells

higher levels of MHC expression products (human leukocyte antigen, HLA) [54]. More new antigens with sufficient immunogenicity are produced in responders, whereas non-responders may be resistant to treatment because of the lack of tumour immunogenicity [55].

Dysfunction of MHC

Antigen presentation of melanoma cells occurs mainly through the MHCI pathway in TME (tumor cells can activate T cells through MHCI pathway); therefore, tumour cells can evade T cell-mediated killing through the inactivation of MHC-I. β2-microglobulin (B2M) is closely related to the production and stability of the HLAI complex [56]. Some studies have shown that B2M mutation can lead to HLAI dysfunction, which affects antigen presentation and eventually weakens the cytotoxicity of T cells [57]. In a study, after anti-PD-1 therapy, the incidence of B2M gene mutation was three times higher in non-responders than in responders [58]. Therefore, melanoma cells may resist the action of PD-1 inhibitors by interfering with MHC-I function through B2M mutations.

Emergence of T-cell exhaustion

Owing to the long-term existence of tumour antigens and immunosuppression in TME, T cells may gradually lose their effector function, thus exhibiting a state called 'exhaustion'. During T-cell exhaustion, effector T cells (Teffs) are also called depleted T cells (Tex) [59]. Studies have shown that under the continuous stimulation of tumour-derived vascular endothelial growth factor (VEGF), $CD8^+$ T cells show a state of 'failure' and express various inhibitory receptors, including PD-1, T cell immunoglobulin and mucin domain-containing 3 (TIM3), lymphocyte activation gene 3 (LAG3) and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) [60, 61]. In addition, the abundance of PD1 expressed on T cells affects the efficacy of anti-PD-1 therapy, and exhausted $CD8^+$ T cells expressing high levels of PD-1 cannot respond to PD-1 inhibitors [62, 63]. This is because terminal Tex is a kind of dysfunctional cells with high expression of inhibitory receptors and little response to specific antigens. Previous studies have suggested that the blockage of PD-1 pathway can reverse terminal Tex in chronic infection into functional T cells [59, 64]. However, subsequent studies have pointed out that the epigenetic state of terminal Tex is difficult to be changed, which means that Immune checkpoint blockade (ICB) can hardly reverse the state of terminal Tex [65].Therefore, T-cell exhaustion is an important phenomenon underlying the resistance to PD-1 inhibitors.

Resistance to IFN-γ signal

The IFN-γ pathway in tumour cells plays both beneficial and detrimental roles in immunotherapy. T cells produce IFN-γ by recognising receptors on the surface of tumour cells, which can not only increase the expression of MHC molecules to enhance tumour antigen presentation and recruit immune cells but also directly inhibit the proliferation of tumour cells and promote apoptosis [66]. The continuous expression of IFNs can affect the immune editing of tumour cells, which may lead to immunotherapy resistance [67, 68]. In addition, silencing or mutation of genes involved in the IFN-γ pathway, such as JaK1/JaK2 and STATS, can suppress the anti-tumour effects of IFN-γ [69–71] and PD-L1 expression in tumour cells. In such cases, although patients with melanoma with a high tumour mutational burden (TMB) are eligible for anti-PD-1/PD-L1 therapy, anti-PD-1 therapy is not effective. At present, there are two main ways of immunotherapy for IFN- γ pathway. The first is for tumors without IFN- γ signal, which leads to PD-L1 or PD-1 antibody resistance due to the lack of adaptive expression of PD-L1. Activating the alternative interferon pathway (type I IFN) mainly through TLR agonists, oncolytic viruses, or other pathways may also lead to the activation of signal transducer and activator of transcription 1 (STAT1) and STAT2 signals, thus promoting the transcription of PD-L1 and MHC class I by inducing interferon regulatory factor 1 (IRF1) [72]. The second method is for tumors that have been exposed to IFN- γ for a long time (such as ultraviolet-induced malignant melanoma of the skin), which is generally treated with systemic blocking of IFN- γ [73]. Both methods can effectively enhance the efficacy of immune checkpoint inhibitors and reduce their drug resistance.

Mitochondrial autophagy

Some recent studies have reported that mitochondrial autophagy can affect the role of PD-1 inhibitors. T cells can induce melanoma cell apoptosis by mediating tumour necrosis factor-alpha (TNF-α) signalling. Nuclear factor kappa B (NF-κB) signalling and autophagy play an important role in melanoma cell protection [74, 75]. In a study, T cells were more lethal to melanoma cells after a single autophagy-related gene (CRISPR) was knocked out; however, increased autophagy activity protected tumour cells from T cell-mediated killing [76, 77]. Therefore, targeting mitochondrial autophagy may enhance immunotherapy sensitivity in melanoma.

Mitochondrial metabolites affect the expression of PD-1 on T cells

Some mitochondrial metabolites in melanoma cells, such as NAD^+, glucose and glutamine, can promote tumour immune escape. PD-L1 expression has been associated with the content of NAD^+ and glucose [78, 79]. Glutamine and glucose are indispensable to the development and activation of Teff cells [80]. However, in vivo studies have shown that high expression of PD-1 on the surface of Tregs may be an important factor leading to primary resistance to PD-1 inhibitors [81]. Compared with effector T cells, Treg cells can use Monocarboxylate transporter-1 (MCT1) to efficiently uptake lactic acid in tumor microenvironment with abnormally elevated glycolysis levels, promote the entry of NFAT1 into the nucleus and induce Treg cells to express PD-1, while the expression of PD-1 on $CD8^+$T cell will be inhibited, resulting in the failure of PD-1 immunoblocking therapy. This reveals a new way in which lactic acid metabolism affects tumor immune microenvironment, and provides a new idea for developing new tumor immunotherapy strategies targeting lactic acid metabolism (such as MCT1, LDHA) [82, 83].

Interference of other factors between TME in melanoma

The microenvironment around melanoma cells contains a large number of cytokines, tumour metabolites and immunosuppressive cells that resist the anti-tumour effects of the immune system and promote the growth, reproduction and invasive ability of tumour cells [84, 85]. Tregs in TME can reduce the content of IL-2 in TME and promote the expression of CTLA4 by producing immunosuppressive components such as TGF-β, IL-10 and extracellular adenosine, thus inhibiting the physiological function of $CD8^+$ T cells and favouring immune evasion of melanoma cells [86]. Additionally, tumour-associated myeloid-derived suppressor cells (tumour-MDSCs) and tumour-associated macrophages (TAMs) have also been associated with resistance to PD-1 inhibitors. Some studies have found that the expressions of Tyro3, Ax1, MERTK and their ligands of MDSCs in tumor-bearing (melanoma) mice are significantly up-regulated, which can inhibit the ability of T cells to migrate to tumor draining lymph nodes. Interestingly, when drugs inhibit the expression of Tyro3, Ax1 and MERTK in vivo, melanoma growth slows down, $CD8^+$T cell infiltration increases, and anti-PD-1 checkpoint inhibitor immunotherapy is enhanced. This suggests that Tyro3, Ax1 and MERTK control the function of MDSC and are expected to be pharmacological targets for regulating MDSC-mediated immunosuppression in patients with melanoma [87]. As a kind of immunosuppressive cells, TAMs can lead to T cell dysfunction and failure by expressing homologous immunoassay ligands (PD-L1) and secreting cytokines and metabolites (such as TGF- β, PGE2) [88–90]. Therefore, TAMS may also be an important target for reversing anti-PD-1 drug resistance.

Mitochondria and melanoma

Mitochondria are a type of organelle surrounded by two membranes in eukaryotic cells. They produce energy and are the primary site of aerobic respiration. Their diameter is approximately 0.5–1.0 microns. As semi-autonomous organelles, mitochondria have genetic material and a genetic system, namely, mitochondrial DNA (mtDNA); however, their genome size is limited. In addition to producing > 90% ATP to provide energy for cells through oxidative phosphorylation under aerobic conditions, mitochondria are involved in processes such as cell differentiation, information transmission and apoptosis, and can regulate cell growth and cell cycle [91, 92].

During the occurrence and development of melanoma, the functional changes in mitochondria are related to tumour cell proliferation, metastasis and resistance to targeted therapy [93]. Cells in the tumour centre lack oxygen because they are distant from the blood supply and may be more dependent on glycolysis [94, 95]. Glycolysis may benefit the survival of tumour cells under hypoxic conditions. Moreover, hypoxia can reduce the efficacy of radiotherapy, immunotherapy and chemotherapy [96]. Even under aerobic conditions, the glycolytic pathway in melanoma cells may enhance the resistance to radiation and chemotherapy by activating NF-κB, thus promoting cell survival [97]. Multiple mitochondrial responses and metabolic changes may also promote resistance to targeted therapy [98] (Fig. 2).

The metabolic changes of tumor cells have always been considered to be closely related to mitochondria [99]. According to the Warburg theory, tumour cells gradually replace mitochondrial oxidative metabolism with glycolysis, thus promoting their rapid proliferation. Melanoma cells often show the characteristics of the classical Warburg effect, with some cells also maintaining high levels of disordered oxidative phosphorylation (OXPHOS). Therefore, inhibition of glycolysis and disordered OXPHOS plays a key role in the treatment of melanoma [100–102]. To date, some drugs with mitochondria-targeting function have been used in experiments or clinics (Table 2). Factors affecting the function of mitochondria in melanoma cells are described below (Fig. 3).

Mutations in mitochondrial DNA(mtDNA)

There is a set of genetic material in mitochondria independent of nucleus-mtDNA. The length of human mitochondrial DNA is 16569 bp, which has 37 genes and encodes 13 proteins. These proteins are involved in cell

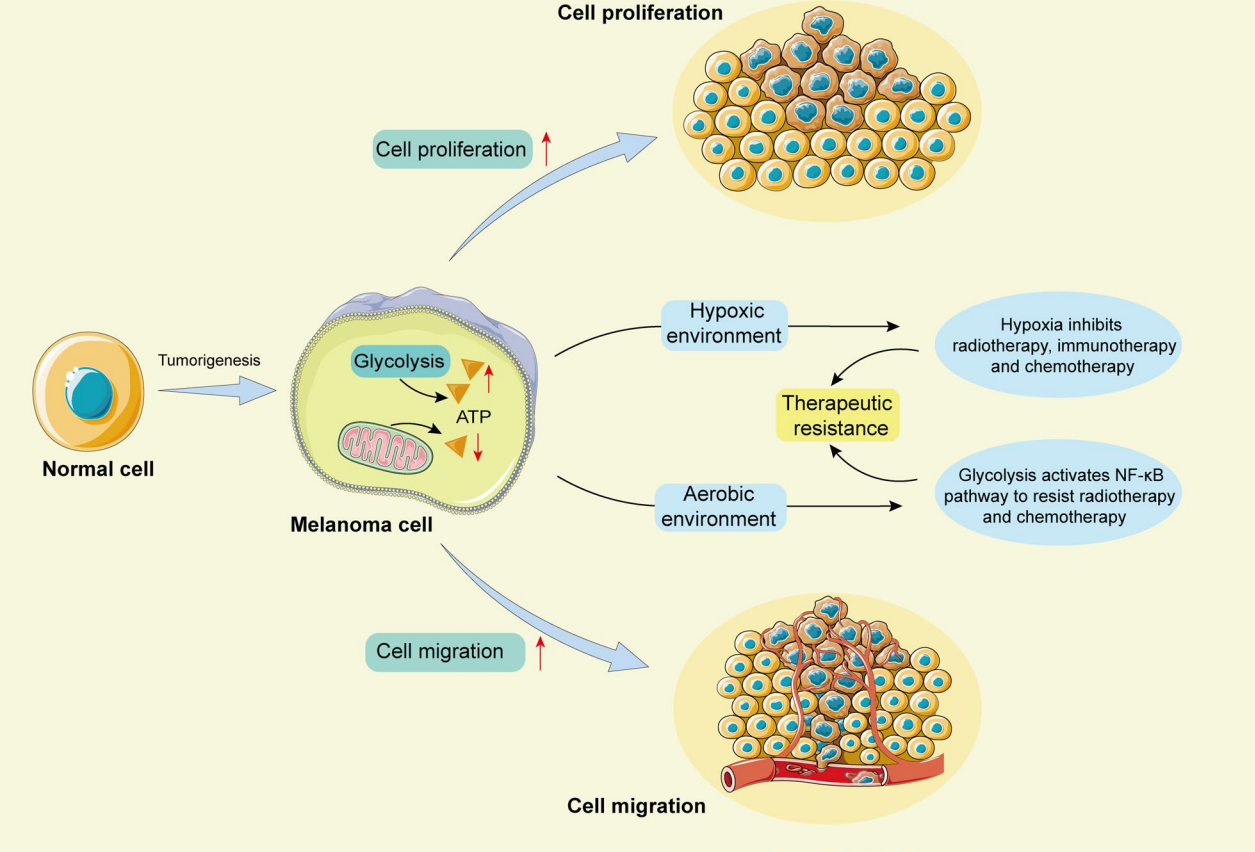

Fig. 2 Metabolic changes in melanoma cells affect cell proliferation, migration and therapeutic resistance. When normal cells are transformed into melanoma cells, intracellular mitochondrial metabolism is weakened and glycolysis is enhanced, which will promote tumor cell proliferation, migration and therapeutic resistance

energy metabolism [142, 143]. Owing to the lack of protective tissue proteins and related mechanisms of DNA repair, mtDNA has a much higher mutation rate than nuclear DNA under the influence of ROS [144]. Therefore, to maintain their normal function and protect their genome, mitochondria usually respond to genotoxic damage by increasing mtDNA production. [145]. In melanoma cells, the persistent stimulation of mitochondria by AKT protein leads to a decrease in mitochondrial function and an increase in ROS production. Consequently, mtDNA is under oxidative stress for a long time, and ROS can induce oxidative mtDNA (Ox-mtDNA) production [146]. In mitochondria, Ox-mtDNA is either repaired by DNA glycosylase OGG1 or escaped through an open permeability transition pore (mPTP) on the outer membrane of the mitochondria. However, oxidized mtDNA is so large that it needs to be cut into smaller fragments before it can pass through the conversion hole, and this step is done by an enzyme called FEN1. Once cleaved by FEN1, Ox-mtDNA fragments escape through mPTP and enter the cytoplasm, and then they bind to two key factors: nod-like receptor heat protein domain related protein 3 (NLRP3) and cyclic GMP-AMP synthase (cGAS) [147]. The combination of Ox-mtDNA with NLRP3 and cGAS can not only induce inflammation, but also induce the transcription of PD-L1 in melanoma cells, which leads to immune escape. Therefore, we believe that the activation of T cells can be promoted by inhibiting the release of Ox-mtDNA [148, 149]. Some studies have reported that in addition to mtDNA mutations, DNA fixes defects and replication errors also lead to abnormal mitochondrial function and eventually promote the malignant transformation of tumours [150].

Mitochondria are matrilineal organelles that originate from symbiotic bacteria. They coevolve with their hosts, so most mitochondrial proteins are nuclear-encoded. Mitochondrial Lon peptidase 1 (LONP1) is an ATP-dependent protein encoded by nuclear DNA. It is located in the mitochondrial matrix and plays an important role in regulating mitochondrial gene expression and maintaining mitochondrial stability [151]. Some studies have demonstrated that LONP1 expression is significantly

Table 2 Studies on the treatment of melanoma by affecting the function of mitochondria

Melanoma type	Reagent	Mechanism	References
MAPK mutation	Talimogene laherparepvec(T-VEC)	Oncolytic virus	[36]
	Prenyl-binding protein phosphodiesterase-δ (PDEδ)	NRAS inhibitor	[103]
	Vemurafenib	BRAF inhibitor	[104]
	Dabrafenib	BRAF inhibitor	[105]
	Encorafenib	BRAF inhibitor	[106]
	Sorafenib	BRAF inhibitor	[107]
	Trametinib	MEK inhibitor	[108]
	Cobimetinib	MEK inhibitor	[109]
	Binimetinib	MEK inhibitor	[110]
mtDNA/DNA mutation	Temozolomide (TMZ)	DNA alkylating agent	[111]
	Fotemustine (FM)	DNA alkylating agent	[112, 113]
	Carboplatin/Cisplatin	DNA alkylating agent	[114, 115]
	Dacarbazine (DTIC)	DNA alkylating agent	[116]
	VAS2870	NADPH oxidase inhibitor, Reduce ROS	[117]
	Diphenylene iodonium (DPI)	NADPH oxidase inhibitor, Reduce ROS	[118, 119]
	Irinotecan	Reduce ROS	[120]
	Apocynin (4-Hydroxy-3-methoxyacetophenone)	PI3K inhibitor, Reduce ROS	[121]
Drp1 expression disorder	Vemurafenib	Inhibition of Drp1 phosphorylation	[122]
	Cryptolepine	Drp1 inhibitor	[123]
	mitochondrial division inhibitor-1 (MDIVI-1)	Drp1 inhibitor	[124, 125]
Calcium signal expression disorder	Diallyl trisulfide	Induce mitochondrial Ca^{2+} overload	[126]
	δ-tocotrienol	Induce mitochondrial Ca^{2+} overload	[127]
	Luteolin	Induce tumor cell death	[128]
	N-acetyl-S-(p-chlorophenylcarbamoyl) cysteine (NACC)	Induce tumor cell death	[129]
	Sanguinarine	Induce tumor cell death	[130]
	Aripiprazole	Depletion of endoplasmic reticulum calcium	[131]
	Digitoxin	Alter mitochondrial membrane potential	[132]
	Lmiquimod	Induce Ca^{2+} depletion	[133, 134]
Abnormal tumor mitochondria OXPHOS	Metformin	OXPHOS inhibitor	[135, 136]
	Atovaquone	OXPHOS inhibitor	[135]
	Arsenic trioxide	OXPHOS inhibitor	[135]
	ONC212	OXPHOS inhibitor	[100]
	Mito-MGN	OXPHOS inhibitor	[101]
	MITO-ONC-RX	OXPHOS inhibitor	[137]
	Chitosan biguanide	Mitochondrial function inhibitor	[138, 139]
	Phenformin	Mitochondrial function inhibitor	[140]
	Sorafenib	Mitochondrial function inhibitor, inducing tumor vessel normalization	[141]

increased in melanoma and is related to changes in the metabolic mode of melanoma cells [152]. Overexpression of LONP1 promotes the progression of melanoma, whereas its knockdown inhibits tumour growth and migration. However, if the protein expression of LONP1 is too low, it may lead to mitochondrial dysfunction, thereby promoting the occurrence and development of melanoma [152]. Due to the close communication between mitochondria and nuclei (Cross-talk), in which mtDNA may reverse regulate nuclear gene transcription, the anti-tumor mechanism of mitochondrial therapy may be related to mitochondrial-nuclear interaction. Microarray analysis showed that mitochondria could regulate several carcinogenic pathways, such as cyclin D1, ras, src and p53, and participate in its anti-tumor effect [153, 154].

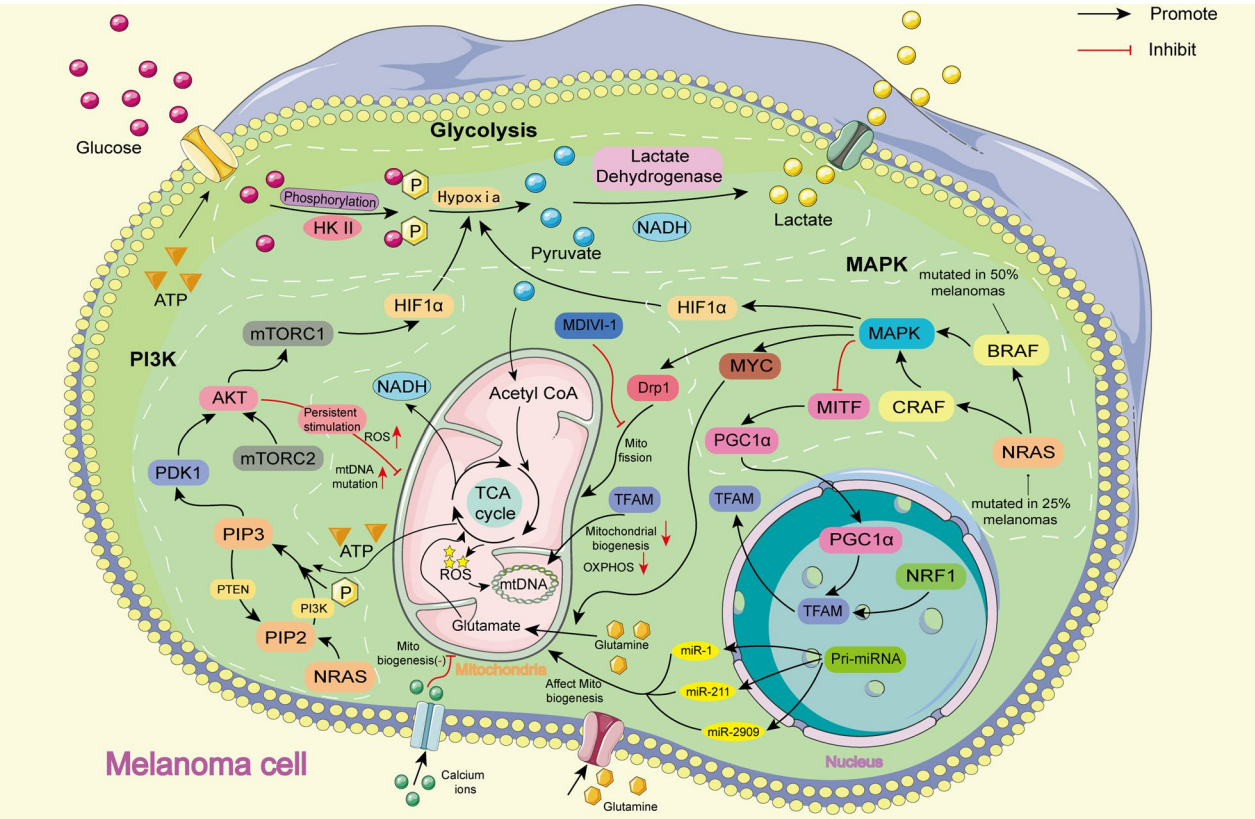

Fig. 3 The relationship between the occurrence and development of melanoma cells and mitochondria. Activation and mutation of NRAS or BRAF genes in MAPK and PI3K signaling pathways in melanoma cells can inhibit mitochondrial function and promote glycolysis. The increase of intracellular calcium concentration in melanoma cells can inhibit the function of mitochondria. In addition, some miRNAs may also affect the function of mitochondria. PI3K: Phosphatidylinositol 3-kinase; MAPK: Mitogen-activated protein kinases; NADH: Nicotinamide adenine dinucleotide; HIF1α: Hypoxia inducible factor-1α; mTOR: mammalian Target of rapamycin; PDK1: Phosphoinositide-dependent protein kinase 1; PTEN: Phosphatase and tensin homolog; NRAS: Neuroblastoma RAS; MAPK: Mitogen-activated protein kinase; MITF: Microphthalmia-associated transcription factor; NRF1: Nuclar respiratory factor-1; TFAM: Mitochondrial transcription factor A; MYC: Myelocytomatosis viral oncogene; Drp1: Dynamin-related protein 1; MDIVI-1: Mitochondrial division inhibitor 1

Mutations in the BRAF or NRAS gene

During the formation and development of melanoma, mutations in some genes that affect mitochondrial oxidative metabolism may promote the proliferation and survival of melanoma. Activating mutations in the NRAS and BRAF genes play an important role in promoting the progression of melanoma [155].

NRAS gene is located upstream of multiple signalling pathways. Activating mutations in the NRAS gene not only affect the MAPK signalling pathway but also activate PI3K signal transduction [156, 157]. Both MAPK and PI3K pathways eventually promote glycolysis and inhibit mitochondrial oxidative metabolism in melanoma. In addition, clinical studies have shown that melanoma with activating mutations in the NRAS gene is highly invasive and can rapidly develop resistance to existing treatment strategies [155, 158].

Mutation at V600E in the BRAF gene ($BRAF^{V600E}$ mutation) in melanoma cells can promote glycolysis to absorb and integrate substances required for tumour cell proliferation. Additionally, $BRAF^{V600E}$ mutation decreases the expression of PGC-1α by inhibiting the activity of MITF [159]. Some studies have shown that a decrease in the protein expression of PGC-1α can decrease the energy metabolism of mitochondria and increase the content of ROS in the cytoplasm in melanoma. [160]. In addition, $BRAF^{V600E}$–MAPK signalling can regulate mitochondrial function and induce mitochondrial division by activating the expression of dynamin-related protein 1 (Drp1) in melanoma [161].

Changes in mitochondrial function

The occurrence and development of melanoma is often accompanied by changes in mitochondrial function. In

normal somatic cells, a delicate balance exists between mitochondrial division and fusion to maintain proper mitochondrial function [162]. Mitochondrial division is mainly mediated by Drp1, whereas mitochondrial fusion is mediated by dynamic-associated proteins, including Mfn1, Mfn2 and OPA1 [163]. Mitochondrial division in mammalian cells is controlled by Drp1 [161, 164]. During mitochondrial division, Drp1 is transported from the cytoplasm to the mitochondrial outer membrane and binds to fission-1 (Fis1) and mitochondrial fission factor (Mff) located in the mitochondrial outer membrane [165]. During mitochondrial fusion, it is affected by the mitofusin-1/2 gene (Mfn1 and Mfn2) located in the outer membrane of mitochondria and OPA1 in the inner membrane of mitochondria [125]. However, unlike in normal cells, in melanoma cells with activated MAPK mutations, the deletion of Drp1 initiates mitochondrial network reprogramming, induces mitochondrial superfusion and promotes mitochondrial oxidative metabolism [125, 161]. Some studies have shown that mitochondrial division increases in melanoma and mitochondrial fusion may be directly related to chemotherapy resistance [166]. Therefore, changes in mitochondrial dynamics may be a potential target for adjuvant chemotherapy in melanoma.

Mutations in genes involved in the MAPK pathway are most common in melanoma with changes in mitochondrial function, including activating mutations in the BRAF gene, NRAS gene and tyrosine kinase (such as KIT) and inactivating mutation in the NF1 gene [167–170]. These mutations can inhibit the expression of a transcription factor called microphthalmia-associated transcription factor (MITF) in the TME of melanoma. However, MITF can influence the biogenesis and functional regulation of mitochondria by promoting the expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), In addition, the mitochondrial master regulator PGC-1α is associated with the phenotypic transition between proliferation and invasion, which is attributed to different downstream activation signalling pathways [93, 171, 172]. Activation of the PI3K pathway leads to the formation of PIP3. Simultaneously, phosphorylation and activation of AKT by phospholipid-dependent kinase-1 (PDK-1) can directly or indirectly activate mTOR, which in turn induces the expression of hypoxia-inducible factor-1α (HIF1α) [173]. HIF1α inhibits mitochondrial respiration and promotes glycolysis [174]. The mechanisms underlying the occurrence and development of melanoma and related signalling pathways have been identified through large-scale sequencing [175]. Changes in the MAPK and PI3K pathways are more commonly attributed to the occurrence of melanoma and can significantly affect the metabolism of melanoma cells. Additionally, the AMP-activated protein kinase (AMPK) pathway involved in mitochondrial function has been associated with the metabolism of melanoma cells [176, 177]. AMPK is a well-known metabolic receptor that maintains cellular energy homeostasis. It senses the energy content of mitochondria through direct interaction with adenosine triphosphate (ATP), adenosine diphosphate (ADP) and adenosine monophosphate (AMP) [178]. When OXPHOS is inhibited in mitochondria, AMPK can bind to PD-L1 in the endoplasmic reticulum (ER) and phosphorylate PD-L1 at S195, thus reducing the content of PD-L1 in tumour cells [179–181]. In melanoma cells, mutations in a signal pathway can regulate the function of mitochondria, thus affecting the balance of cell metabolism. Therefore, mitochondria play an important role in the occurrence and development of melanoma.

Other mechanisms

Micro-ribonucleic acids (miRNAs) are promising targets for cancer therapy and may be used as molecular biomarkers of drug resistance in melanoma. Some studies have demonstrated that miR-1 overexpression can induce mitochondrial autophagy in melanoma stem cells (MSCs) by directly targeting the glycerol-3-phosphate dehydrogenase 2 (GPD2) gene and the 3′-UTR of mitochondrial inner membrane tissue system 1 (MINOS1) and interacting with a mitochondrial protein (LRPPRC) [182]. miR-211, which is a tumour suppressor, acts as a metabolic switch and is downregulated in patients with melanoma. Some studies have reported that deletion of miR-211 can lead to downregulation of the TCA cycle and OXPHOS, thereby inhibiting the metabolic function of mitochondria [183]. Additionally, mitochondrial dysfunction associated with the imbalance of miR-2909 expression can lead to the Warburg effect in melanoma [184]. Barbato et al. used integrative genomic analysis and identified the miR-181/TFAM pathway as a key driver of drug resistance in melanoma [185].

Calcium signalling is a major focus of research on anti-tumour therapy. It plays an important role in the pathological status of melanoma. Intracellular calcium concentration, expression of calcium-related signalling proteins, calcium channels on the cell membrane and the Wnt/Ca^{2+} pathway are related to the occurrence and development of melanoma [186, 187]. Evidence documents that increased intracellular calcium stores are associated with highly metastatic melanoma cells [186]. Y-box binding protein 1(YB-1) is an unfavorable prognostic marker secreted from melanoma depending on [Ca^{2+}] i and ATP levels, the expression of which increases in primary and metastatic melanoma, compared to benign melanocytic nevi. Interestingly, elevated YB-1 secretion stimulates melanoma cell migration, invasion, and

tumorigenicity [188]. It has been reported that Calcium channel dynamics are implicated in melanoma treatment targeting mitochondria stress [189]. Some drugs with anti-melanoma effect (such as diallyl trisulfide) can cause voltage-dependent calcium channel (VDCC)-mediated mitochondrial Ca^{2+} overloa, ROS production and caspase activation, thus inhibiting the biological progression of melanoma [126, 190]. In some conditions, targeting calcium signaling is able to render melanomas more susceptible to conventional therapy, preventing the development of drug resistance and providing novel ideas for combination treatment. For example, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising anticancer drug, while some melanomas are resistant to TRAIL therapy. Studies have shown that Ca^{2+} dynamics are a promising approach to overcome TRAIL resistance. Mitochondrial calcium removal can increase the efficacy of TRAIL in the treatment of melanoma through mitochondrial hyperfusion [186]. Therefore, we speculate that targeted calcium signal combined with anti-PD-1 therapy is a potential treatment for melanoma.

Mitochondria and T cells

Changes in mitochondrial function in melanoma cells can directly affect the development of melanoma, whereas those in immune cells can indirectly affect the progression of melanoma. T lymphocytes are the final effector cells in immune checkpoint inhibitor (ICI)-based immunotherapy, and the number of T cells infiltrating the tumour site is an important indicator of the efficacy of ICI therapy [191, 192]. PD-1 is not only a major regulator of immune homeostasis but also one of the immune checkpoint (IC) molecules [193]. Recent studies have shown that melanoma cells can evade immune surveillance by expressing PD-L1, interacting with PD-1 on T cells and maintaining T cells in a resting state by inhibiting T-cell energy metabolism [194]. In TME, the energy metabolism of mitochondria in T cells plays a key role in regulating anti-tumour immune responses. T cell proliferation requires mitochondrial metabolism, production of ATP for biosynthesis, signal pathways, production of ROS, and activation of NFAT (a key transcription factor produced by IL-2) [195, 196].

Because the metabolism of cells is inseparable from the biological function of mitochondria, the relationship between PD-1 and mitochondria can be recognised from the perspective of cellular bioenergetics. PD-1 is not expressed on immature T cells, which have low metabolic activity and mainly depend on the tricarboxylic acid (TCA) cycle and OXPHOS pathway [197, 198]. During the normal development of T cells, after PD-1 is activated, the metabolism of T cells is temporarily dominated by glycolysis to meet the sudden increase in energy demand [199]. When T cells are required to play an immune-related role, they usually differentiate into Teffs, memory T (TM) cells and Tregs. Teffs (such as $CD8^+$ T lymphocytes) can directly kill tumour cells, resulting in upregulation of the TCA cycle and OXPHOS in cells and a decrease in the expression of PD-1 [200, 201]. In an in vitro study, activation of PD-1 decreased the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), indicating that activation of PD-1 reduced the mitochondrial energy metabolism of T cells [202, 203]. In addition, PD-1 activation can affect mitochondrial function by inhibiting the AKT and mTOR pathways located downstream of TCR [204]. However, owing to the long-term presence of tumour antigens and immunosuppression in TME, T cells may gradually 'fail' and lose their function. During T-cell exhaustion, the expression of PD-1 on Teffs is upregulated, and intracellular metabolism shifts to glycolysis [197, 198, 205]. After the TCR–MHC pathway is activated, melanoma-specific $CD8^+$ T cells upregulate aerobic glycolysis to support their rapid proliferation and anabolism [206, 207]. Simultaneously, the PI3K–Akt–mTOR signalling pathway is activated, which promotes the secretion of IFN-γ from $CD8^+$ T cells, thereby enhancing the anti-tumour function of T cells [208]. However, compared with melanoma cells, T cells have a significantly weak glycolytic ability, which suppresses the anti-tumour function and eventually triggers immune escape [209, 210].

TM cells or Tregs mainly rely on the metabolic pathway of OXPHOS to survive and can inhibit the expression of PD-1 by activating AMPK, thus maintaining the balance of intracellular metabolism [197, 211, 212]. However, contrary to Teff cells and TM cells, Tex cells exhibited metabolic deficiency, including glucose uptake and decreased OXPHOS, some studies have shown that early Tex cells can restore certain proliferation and immune response by activating OXPHOS [213, 214]. In addition, $CD8^+$TILs have been shown to lose mitochondrial activity and biogenetic ability due to the decreased expression of transcriptional coactivator PGC-1α, which plays a key role in mitochondrial biogenesis and antioxidation. In B16 mouse tumor model, overexpression of PGC-1α in tumor specific $CD8^+$T cells can increase the biogenesis and maintain the effect function of mitochondria, and effectively inhibit tumor activity [214]. Therefore, we speculate that activating the mitochondrial function in effector T cells may inhibit the occurrence of immune escape.

It is well known that calcium channel kinetics is associated with the treatment of melanoma for mitochondrial stress. At present, it has been proved that the increase of $[Ca^{2+}]$ i mediated by SOCE can promote the cytotoxicity mediated by cytotoxic T lymphocytes

(CTL) in melanoma [215]. However, based on the tumor immune monitoring of T cells, we found that regulatory T cells can inhibit the production of IP3 through TGF- β, reduce the intracellular calcium flow, lead to the death of effector T cells, inhibit the activation of T cells, and induce immunosuppression. Interestingly, when enhancing the high selectivity of calcium signal in CTL or knocking out EGR4 in T cells (EGR4, a member of the zinc finger transcription factor family, was reported as a key regulator of T cell differentiation), IFN- γ production is increased, T cells are activated and melanoma growth is inhibited [216, 217]. Therefore, we speculate that targeting calcium signal combined with anti-PD-1 therapy will be a new hope for melanoma patients.

Functional changes in mitochondria and resistance of melanoma to PD-1 inhibitors

In recent years, anti-PD-1 therapy has emerged as one of the main therapeutic strategies for melanoma. However, most patients do not exhibit a clinical response to PD-1 inhibitors, and those who respond subsequently acquire drug resistance [16, 22, 23]. At present, some researchers have sorted out the effects of internal and external factors of tumor patients on ICB response, drug resistance and toxicity, and put forward the idea of improving the efficacy of ICB by affecting the function of cells in TME [218, 219]. Changes in mitochondrial function in tumour and immune cells in melanoma resistant to PD-1 inhibitors and the effects of other cells in TME on drug resistance are described below (Fig. 4).

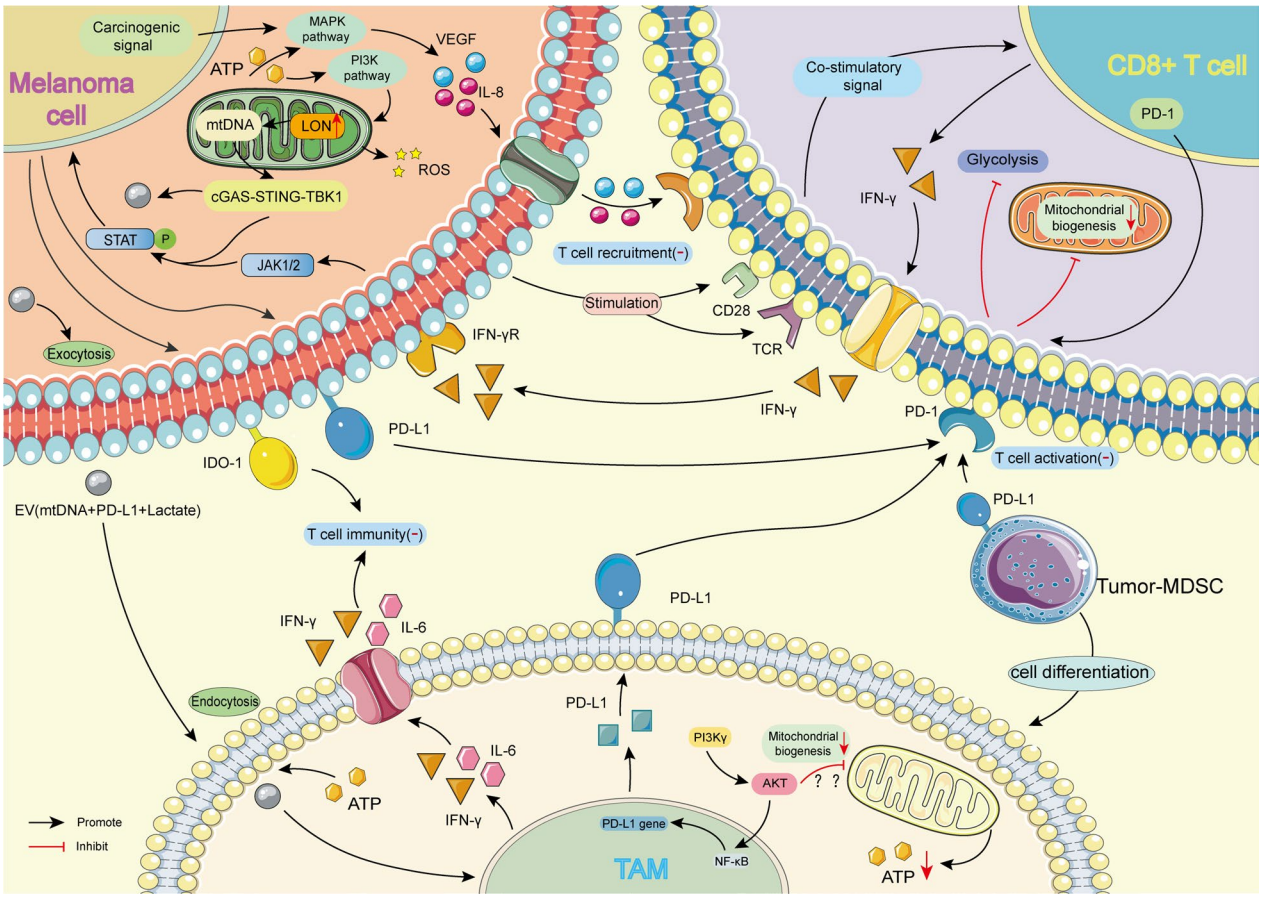

Fig. 4 Changes of mitochondrial function in different cells during drug resistance of melanoma TME. Melanoma cells, Tumor-MDSCs, and TAMs can all express PD-L1, which makes $CD8^+$ T cells in a resting state. Among them, the expression of PD-L1 in melanoma cells is related to the JAK1/2-STAT pathway involved in mitochondria, while the expression of PD-L1 in TAM may be related to the PI3K γ-NF κ B pathway. When $CD8^+$T cells receive dual-signal stimulation from melanoma cells, they can release IFN- γ to participate in immune regulation. After receiving the extracellular carrier (EV) released by melanoma cells, TAMS also releases interferon-γ and IL-6 to inhibit the immune function of T cells. In addition, melanoma cells can inhibit T cell aggregation by producing VEGF and IL-8 through the MAPK pathway, affecting their mitochondria's function through the PI3K pathway. Tumor-MDSCs: Tumor-associated myeloid-derived suppressor cells; TAM: Tumor-associated macrophages; IFN- γ: Interferon-gamma; VEGF: Vascular endothelial growth factor; IDO-1: Indoleamine 2,3-Dioxygenase-1; EV: Extracellular vesicle

Changes in mitochondrial function in tumour cells

The abnormal expression of some genes and dysfunction of some pathways in tumour cells are internal factors leading to immunotherapy resistance in solid tumour cells (including melanoma). These factors may be active before immunotherapy (primary drug resistance) or may be a result of exposure to immunotherapeutic drugs (acquired drug resistance).

Compared with the metabolism of normal melanocytes, that of melanoma cells is dominated by glycolysis [135]. In the previous sections of this review, we mentioned that changes in mitochondrial energy metabolism in melanoma cells may be one of the causes of drug resistance. Metabolic reprogramming from OXPHOS to glycolysis in tumour cells is caused by the mutation of some genes involved in the MAPK pathway and the continuous expression of HIF1α [220, 221]. Carcinogenic signals can also produce proteins (such as VEGF and IL-8) that inhibit T-cell function through the MAPK pathway [222]. As a result, the recruitment of Teffs to the tumour site and immune responses are suppressed. In addition, when the expression of LON is up-regulated, the metabolic function of mitochondria is inhibited and the production of ROS in mitochondria and the level of oxidative stress are increased. Oxidised mtDNA promotes the signal transduction of IFN-γ through the cGAS–STING–TBK1 pathway in the cytoplasm, which leads to the overexpression of IDO-1 and PD-L1 on the surface of tumour cells to inhibit T-cell activation [149]. Consequently, tumour cells develop immune resistance.

As mentioned earlier, when melanoma cells escape immune surveillance through the PD-L1/PD-1 pathway, PD-L1 expressed on melanoma cells binds to PD-1 on the surface of T cells [40]. Prior to this, the antigen peptides produced by melanoma cells transmit 'stimulatory' signals to TCR on the surface of Teffs with the help of APCs. Simultaneously, the B7 family ligands present on APCs bind to CD28 receptors on the surface of Teffs. Under the action of the two types of stimulatory signals, Teffs are activated to kill tumour cells (such as by releasing IFN-γ). Owing to both anti- and pro-cancer functions of IFN-γ, melanoma cells may develop acquired resistance to PD-1 inhibitors [66]. Studies have demonstrated that drug-resistant melanoma cells have lower levels of OXPHOS and lipid metabolism than normal melanoma cells [102]. Therefore, mitochondrial function is further inhibited in melanoma cells resistant to PD-1 inhibitors. These studies suggest that targeted activation of mitochondrial function in melanoma cells combined with anti-PD-1 therapy has become a new treatment strategy for melanoma patients.

Changes in mitochondrial function in T cells

As mentioned earlier, when T cells are required to exert anti-tumour effects, cellular metabolism dominated by mitochondria not only reduces the expression of PD-1 on the cell surface but also promotes the differentiation of T cells [200, 201]. Differentiated T cells play different roles in the development of drug resistance in melanoma. Therefore, changes in mitochondrial function in T cells may lead to drug resistance in melanoma.

Treg infiltration is found in many human tumours, including melanoma [223]. Tregs can inhibit the response of Teffs by secreting inhibitory factors (such as TGF-β, IL-10 and IL-35) or through cellular contact [224–226]. Therefore, Tregs may play an important role in maintaining auto-tolerance [227]. Several animal studies have reported that primary and adaptive drug resistance to immunotherapy can be reduced by affecting the ratio of Teffs-to-Tregs in TME or by directly removing Tregs [228–230]. An in vivo study demonstrated that Tregs can induce high PD-1 expression in $CD8^+$ T cells, leading to primary resistance to PD-1 inhibitors [81]. PD-1 inhibitors usually act on $CD8^+$ T cells, which are activated in the draining lymph nodes (DLNs) and transported to the tumour site through the MIG/CXCR3 axis [18, 231]. Activation of $CD8^+$ T cells is related to Ca^{2+} release, TCA cycle and ROS production [232–234].

Recognition of PD-L1 on the surface of melanoma cells by PD-1 on the surface of T cells inhibits the metabolism of mitochondria in $CD8^+$ T cells. Consequently, $CD8^+$ T cells are in a resting state, allowing melanoma cells to escape immune surveillance [194]. However, the co-inhibition of PD-1 transmission in T cells is blocked in melanoma sensitive to PD-1 inhibitors. The costimulatory signal transmitted by TCR activates intracellular mitochondrial function, thus exerting anti-tumour effects [20, 235]. In melanoma resistant to PD-1 inhibitors, $CD8^+$ T cells irreversibly differentiate into Tex owing to energy depletion, and other mechanisms of drug resistance may directly or indirectly inhibit mitochondrial function in T cells [59, 236, 237]. Studies have demonstrated that the combination of mitochondria-activating agents, such as uncouplers of mitochondrial OXPHOS (FCCP), mTOR activators, AMPK activators and PGC-1α activators, and PD-1 inhibitors can significantly increase the clinical response rate of PD-1 inhibitors [18, 238–240]. We speculate that an inextricable relationship exists between the decreased immune function of $CD8^+$ T cells caused by drug resistance and the inhibited metabolic function of mitochondria in melanoma. To sum up, targeted activation of mitochondrial function in T cells combined with anti-PD-1 therapy can exert a stronger anti-tumor effect and inhibit the occurrence of drug resistance.

Other cells in TME are involved in the resistance of melanoma to PD-1 inhibitors

In addition to melanoma and common T cells, other cell types in the tumour immune microenvironment are involved in the development of resistance to PD-1 inhibitors. Tumour-MDSCs and TAMs have been associated with resistance to PD-1 inhibitors [87, 241]. At present, the relationship between the resistance of melanoma to PD-1 inhibitors and the changes in mitochondrial function in tumour-MDSCs and TAMs remains unclear. However, both MDSCs and TAMs can participate in the immunosuppressive TME by expressing PD-L1 or producing some cytokines in melanoma [87, 241]. Some studies have demonstrated that inhibition of phosphoinositide 3-kinase (PI3K-γ) in macrophages differentiated from tumour-MDSCs can enhance the immunotherapeutic effects of PD-1 inhibitors in mouse models of melanoma [242, 243]. As mentioned earlier, a correlation exists between the activation of PI3K-related pathways and the inhibition of mitochondrial function. In addition, upregulation of LON in the mitochondria of melanoma cells induces the release of extracellular vesicles (EV) carrying mtDNA, PD-L1 and lactic acid from tumour cells to TAMs, thus inducing TAMs to produce IFN-γ and IL-6. This phenomenon weakens T-cell immunity in TME [149].

To the best of our knowledge, no study has examined the changes in mitochondrial function in tumour-MDSCs and TAMs in melanoma resistant to PD-1 inhibitors. However, given that tumour-MDSCs and TAMs are involved in the development of resistance to PD-1 inhibitors in melanoma, we speculate that functional changes in mitochondria in these two types of cells may be related to PD-1 inhibitor resistance.

Conclusion and prospect

At present, PD-1 inhibitors are commonly used to treat melanoma; however, their low response rate remains a problem. To reduce the resistance of melanoma to PD-1 inhibitors and improve the response rate, the combination of PD-1 inhibitors and other therapeutic methods is preferred to the independent use of PD-1 inhibitors [244]. The ability of melanoma cells to resist mitochondria-targeting drugs is reduced because of OXPHOS dysfunction. Therefore, the combination of mitochondrial activators and PD-1 inhibitors may represent a new strategy for the treatment of melanoma in the future [102, 245].

In this review, we summarised the mechanisms underlying the resistance of melanoma to PD-1 inhibitors and discussed therapeutic targets related to mitochondrial function in melanoma cells. In addition, we elucidated the changes in mitochondrial function in different cells in melanoma resistant to PD-1 inhibitors. When drug resistance occurs, mitochondria in both melanoma and immune cells are inhibited, and the development of melanoma is not affected. We hypothesised that in melanoma resistant to PD-1 inhibitors, the use of mitochondria-targeting drugs to activate oxidative metabolism in melanoma and immune cells can not only increase the immune activity of $CD8^+$ T cells (for example, the release of IFN-γ) but also inhibit tumour progression because of the altered energy metabolism balance by downregulating glycolysis. In 2017, Chamoto et al. demonstrated that mitochondria-activating agents can cooperate with PD-1 inhibitors on T cells, resulting in elevated anti-tumour effects [18]. Therefore, the combination of PD-1 inhibitors and mitochondrial activators in the treatment of melanoma is a very promising research direction.

In conclusion, the tolerance of melanoma to PD-1 inhibitors can be reduced by activating mitochondrial function. However, experimental studies should be conducted to verify this viewpoint. We will continue to investigate the immunological mechanisms underlying the abovementioned combination therapy in future trials and will further describe the clinical benefits of this approach for the treatment of melanoma.

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Author contributions

ZZ, FD, and FW contributed to the conception and design of the study. LY performed the statistical analysis. FD wrote the first draft of the manuscript. LY, JL, JW, LF, SD, HL, ML, JW, and ZX wrote sections of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing of interest.

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