Nour *et al. Cancer Cell International* (2025) 25:149
https://doi.org/10.1186/s12935-025-03781-3

Cancer Cell International

REVIEW Open Access

# A new era in melanoma immunotherapy: focus on DCs metabolic reprogramming

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**Abstract**

Melanoma, being one of the most dangerous forms of skin cancer, is characterized by its aggressive and metastatic nature, with the potential to develop resistance to various treatments. This resistance makes the disease challenging to treat, emphasizing the need for new treatment strategies. Within the tumor microenvironment (TME), melanoma cells exploit metabolic shifts, particularly glycolysis, to create an immunosuppressive TME that prevents dendritic cells (DCs) from functioning properly. Essential metabolic alterations such as lactate and lipid accumulation, and lack of tryptophan disrupt DC maturation, antigen presentation, and T cell activation. In recent years, melanoma immunotherapy has increasingly focused on reprogramming the metabolism of DCs. This review paper aims to provide insights into the metabolic suppression of melanoma-associated DCs, allowing the design of therapeutic strategies based on metabolic interventions to promote or restore DC function. This contribution reviews the metabolic reprogramming of DCs as a new approach for melanoma immunotherapy.

**Keywords** Dendritic cell, Melanoma, Metabolic reprogramming, Tumor microenvironment, Immunotherapy

## Introduction

The term 'melanoma' evokes fear among both the public and healthcare professionals. Despite a decrease in the incidence and mortality rates of many cancers in recent years, melanoma cases are on the rise. Currently, melanoma is ranked as the fifth most prevalent cancer in the United States. Although melanoma accounts for only 1% of skin cancers, it is responsible for over 80% of skin cancer-related deaths [1]. Many efforts have been undertaken to improve the morbidity and death rates associated with melanoma, which is considered the most dangerous kind of skin cancer [2]. A complex interplay of genetic susceptibility and environmental exposures contributes to melanoma development. While genetic factors increase the risk of melanoma, the most influential external factor is exposure to ultraviolet radiation, particularly intermittent sun exposure [3, 4]. The treatment landscape of advanced melanoma has transformed remarkably since

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the advent of targeted therapies. This has profoundly impacted the mortality rate. Since 2011, the approval of ten novel targeted immunotherapy agents has led to a nearly 30% decline in mortality rates in the United States [5, 6]. More recently, the clinical efficacy of dendritic cell (DC) vaccines in melanoma has been the subject of much research, having both potential benefits and limitations. DCs are the most effective antigen-presenting cells (APCs). They can activate T lymphocyte responses to specific antigens and are integral to forming anti-tumor immunity [7]. In melanoma, antigen presentation by DCs occurs both in secondary lymphoid organs, such as lymph nodes and within tertiary lymphoid structures (TLSs) that form in the tumor microenvironment (TME). While lymph nodes are the primary site for naïve T cell activation, TLSs are known for their role in shaping local anti-tumor immune responses, containing B cells, $CD8^+$ and $CD4^+$ T cells, and APCs, including DCs, which facilitate local priming and tumor-reactive T cells activation [8]. Melanomas contain a mixed population of DCs, resident Langerhans cells (LCs), and trafficking DCs. LCs, as tissue-resident antigen-presenting cells in the epidermis, act as frontline immune guards, detecting antigens and migrating to draining lymph nodes to initiate immune responses. Trafficking DCs, including conventional DC (cDC) subsets, continuously infiltrate the TME, facilitating T cell activation and shaping adaptive immunity [9, 10]. The presence of TLSs in melanoma is associated with improved patient survival and enhanced responses to immune checkpoint inhibitors, sustaining a functional immune microenvironment. Also, TLSs appear to counteract T cell exhaustion by maintaining populations of memory-like $TCF7^+$ T cells, further supporting their relevance in melanoma immunotherapy [8]. DC vaccines can activate $CD8^+$ cytotoxic T lymphocytes (CTLs), resulting in anti-tumor effects. Studies have shown that DCs can be loaded with tumor-associated antigens, such as those derived from melanoma cells, inducing a strong CTL response [11, 12]. Clinical trials have also reported the DC vaccine's effectiveness in melanoma patients. A phase II trial combining autologous monocyte-derived DC (moDC) vaccination with cisplatin suggested that this approach may enhance tumor-specific immune responses, specifically in advanced melanoma stages [13]. Also, a phase III MIND-DC trial evaluated adjuvant DC therapy in stage IIIB/C melanoma patients. The results showed that treatment was well-tolerated and induced tumor-specific immune responses, but it failed to improve survival outcomes [14]. Despite these achievements, challenges remain regarding the DC vaccine clinical application [15]. Among the critical challenges in this context is the immunoediting phenomenon. In melanoma, immunoediting drives tumor evolution, enabling immune-resistant tumor cells to survive and thrive [16]. Immunoediting is a dynamic process that defines the interaction between the immune system and tumor cells. This occurs in three phases: elimination, equilibrium, and escape [17]. While immune cells, particularly CTLs, recognize and destroy tumor cells, cancer cells can adapt by acquiring mutations and altering their metabolic pathways to escape immune detection. They modify processes such as glycolysis, oxidative phosphorylation (OXPHOS), and lipid metabolism through metabolic reprogramming, creating an environment that supports immune escape. These metabolic changes lead to reduced antigen presentation, increased expression of immune checkpoint molecules like programmed cell death ligand 1 (PD-L1), and the recruitment of immunosuppressive cells. As a result, melanoma cells can effectively evade immune surveillance and continue to proliferate [18]. Moreover, many melanoma patients do not respond to the mentioned treatments, and some may experience disease relapse within the initial months of therapy [19–21], underscoring the need for new therapeutic approaches. Similarly, the use of adoptive cell transfer (ACT) therapies, whether naturally occurring tumor-infiltrating lymphocytes or genetically engineered T lymphocytes, has resulted in complete tumor regression in up to 25% of melanoma patients. However, many patients do not experience any clinical benefits from these treatments [22]. Given the advancements in metastatic melanoma, the need for new therapeutic approaches to broaden treatment options and enhance clinical outcomes remains crucial. Metabolic reprogramming shapes the immune system within the TME. For instance, lipid metabolism is a critical factor that influences the immunosuppressive functions of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), suggesting that targeting metabolic pathways could reshape myeloid cell functions and improve therapeutic outcomes [23, 24]. DC metabolic reprogramming has also been implicated in tumor immune evasion, demanding a deeper understanding and targeting of specific metabolic pathways to overcome immune tolerance mechanisms in melanoma [25]. The potential of DCs to control tumor progression makes understanding their function in the TME of melanoma a key area of research [26]. As immunometabolism governs DC function, this article will review how metabolic influences affect human DCs, underscoring their potential in identifying new therapeutic approaches.

Studies were found using a literature search strategy from PubMed, Scopus, Google Scholar, and Web of Science for all research and review articles related to DC metabolic reprogramming as an immunotherapeutic approach for melanoma. The studies were published from the inception of each database with no language or regional restrictions. The oldest article used in this study is from 2001, and the most recent is from 2025.

The search terms were used according to the combined text and medical subject heading (MeSH) terms in the title and abstract based on the main keywords, including Dendritic cell, Melanoma, Metabolic reprogramming, Tumor microenvironment, and Immunotherapy.

## Metabolic pathways in DCs

DCs are APCs that bridge innate and adaptive immune responses. DCs are strategic immune cells that can shape anti-tumor responses by processing and presenting tumor antigens to T cells [27]. Several recently discovered and essential markers of DCs are known to modulate T cell function and impact the efficacy of immunotherapeutic approaches. New DC markers, such as CD5, CLEC9A (CD370), and XCR1, have been shown to modulate T cell responses. CD5 on type 2 cDCs (cDC2s) regulates inflammatory responses and priming of T cells, while CLEC9A and XCR1 on type 1 cDCs (cDC1s) facilitate cross-presentation of tumor antigens to $CD8^+$ T cells. Other markers, including CD1c (BDCA1) and SIRP-α (CD172a) on cDC2s, enhance $CD4^+$ T cell activation, whereas BDCA2 (CD303) and BDCA4 (CD304) characterize pDCs, which either promote or suppress antitumor immunity [28, 29]. DCs either induce inflammatory or tolerogenic responses, depending on the DC subtype and stimuli they receive from the local environment [30]. Cells utilize nutrients through metabolism to meet their energy and biosynthetic needs for various physiological processes. This metabolic dependency affects the fate of multiple cell types, including DCs [31]. Immature DCs can mature into either immunogenic DCs (iDCs), which promote Th1/Th2/Th17/CTL responses for T cell activation and pathogen elimination, or tolerogenic DCs (tol-DCs, tDCs), which induce regulatory T cell (Treg) expansion and T cell unresponsiveness to maintain immune tolerance [32–34] (Fig. 1; Table 1). Furthermore, the metabolic alterations occurring within the DCs might significantly influence the development of both phenotypes [32].

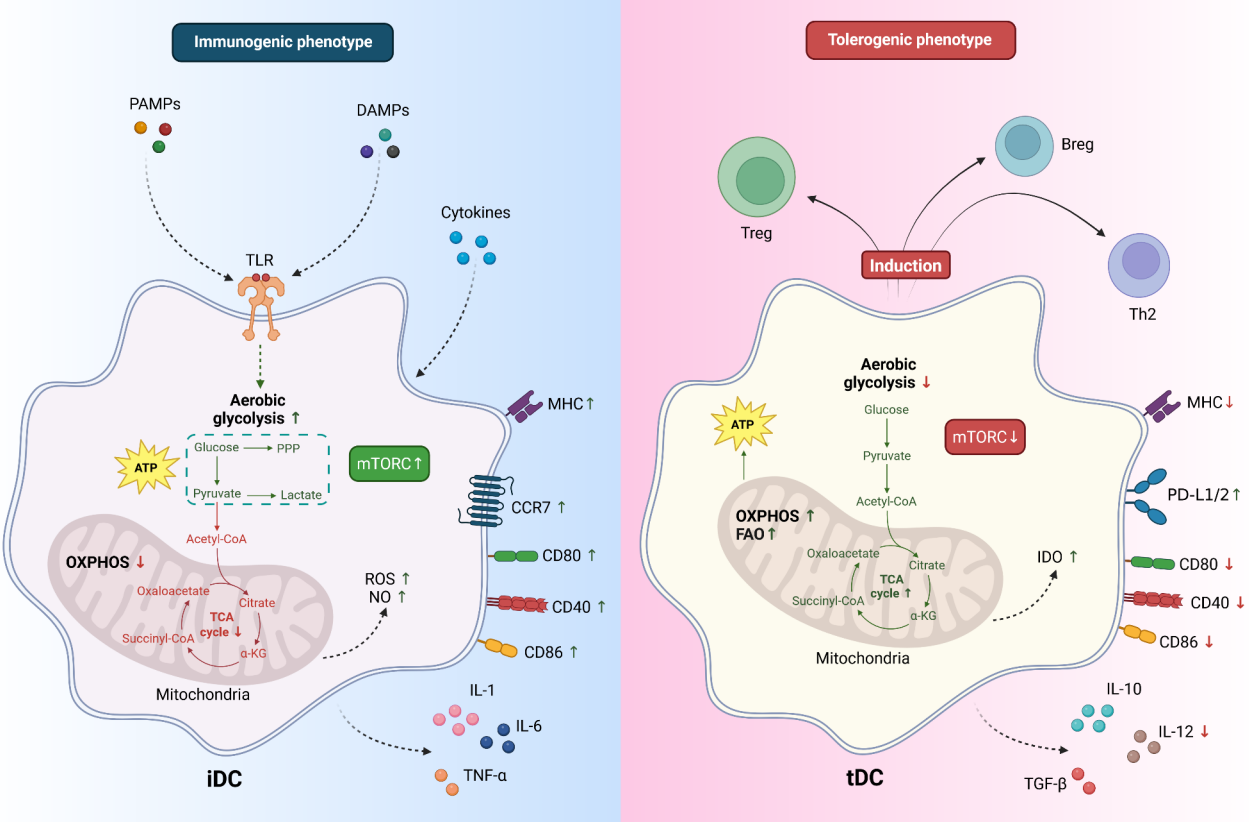


**Fig. 1** Different metabolic pathways in melanoma-associated DCs. DCs exhibit the ability to assume diverse tumorigenic and immunogenic phenotypes as a reaction to the tumor microenvironment and external stimuli. In each case, the cells engage specific metabolic pathways to maximize their functional efficacy. **Abbreviations**: DC: Dendritic cell, iDC: Immunogenic DC, tDC: Tolerogenic DC, IL: Interleukin, TNF-α: Tumor necrosis factor alpha, CD: cluster of differentiation, CCR7: Chemokine receptor type 7, MHC: Major histocompatibility complex, PAMPs: Pathogen-associated molecular patterns, DAMPs: Damage-associated molecular patterns, mTORC: Mammalian target of rapamycin complex, ATP: Adenosine triphosphate, PPP: The pentose phosphate pathway, ROS: Reactive oxygen species, NO: Nitric oxide, TCA: The citric acid cycle, OXPHOS; Oxidative phosphorylation, TLR: Toll-like receptors, Treg: Regulatory T cells, Breg: Regulatory B cells, Th2: T helper 2 cells, PD-L1/2: program cell death 1/2, TGF-β: Transforming growth factor beta, IDO: Indoleamine-pyrrole 2,3-dioxygenase, FAO: Fatty acid oxidation

**Table 1** Comparative metabolic and functional characteristics of iDCs and tDCs

| Aspect | iDCs | tDCs |
|---|---|---|
| **Primary Metabolic Pathway** | Glycolysis: Increased glycolysis for rapid ATP production. | OXPHOS: Relies on mitochondrial respiration and fatty acid oxidation. |
| **Metabolic Shift** | Catabolic to Anabolic: Increased glycolytic flux; lactate production | Catabolic Maintenance: Reduced glycolysis; preserves mitochondrial activity. |
| **Major Cytokines** | Pro-inflammatory: IL-1β, TNF-α, and interferons promote activation | Immunosuppressive: Increased IL-10 and TGF-β; decreased IL-12. |
| **Role in Immune Activation** | T Cell Activation: Promotes CD8+, Th1/Th2/Th17 responses through antigen presentation | Immune Tolerance: Induces Treg expansion and suppresses effector T cell responses. |
| **Surface Markers** | Co-stimulatory Molecules: High expression of CD40, CD80, CD86 | Inhibitory Markers: Lower CD40, CD80, CD86; increased PD-L1, PD-L2. |
| **Immunological Outcome** | Pro-inflammatory Response: Effective T cell priming for pathogen/tumor elimination | Tolerogenic Response: Maintains immune tolerance; promotes Bregs and interacts with Tregs. |
| **Environmental Influence** | Inflammatory Influence: Hypoxia and PAMPs/DAMPs drive glycolysis and migration via CCR7 | Tolerogenic Influence: Interacts with apoptotic cells and TGF-β to maintain tolerance. |
| **mTOR Pathway Involvement** | mTOR Activation: Enhances glycolysis, supporting immunogenic functions | mTOR Inhibition: Promotes OXPHOS and mitochondrial activity, enhancing tolerance. |
| **Key Cellular Processes** | ROS & NO Production: Increased levels support immunogenic signaling | Reduced Glycolysis and ROS: Lower flux and NO production favor tolerogenic functions. |

**Abbreviations**: iDCs: Immunogenic Dendritic Cells, tDCs: Tolerogenic Dendritic Cells, OXPHOS: Oxidative Phosphorylation, IL-1β: Interleukin-1 Beta, TNF-α: Tumor Necrosis Factor Alpha, IL-10: Interleukin-10, TGF-β: Transforming Growth Factor Beta, IL-12: Interleukin-12, Th1/Th2/Th17: T-helper 1/T-helper 2/T-helper 17, Treg: Regulatory T cells, PD-L1: Programmed Death-Ligand 1, PD-L2: Programmed Death-Ligand 2, Bregs: Regulatory B cells, PAMPs: Pathogen-Associated Molecular Patterns, DAMPs: Damage-Associated Molecular Patterns, CCR7: C-C Chemokine Receptor Type 7, mTOR: Mechanistic Target of Rapamycin, ROS: Reactive Oxygen Species, NO: Nitric Oxide

### Immunogenic phenotype

iDCs are generated from various progenitor cells in the bone marrow [35, 36]. Their development is a complex process with several stages, beginning with the differentiation of hematopoietic stem cells into common myeloid progenitors, subsequently giving rise to DC precursors [37]. These precursors can then migrate to peripheral tissues, where many antigens and signals can promote their maturation into fully functional iDCs [38]. The maturation process and functional characteristics of iDCs are affected by their setting, including pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and cytokines. In this regard, exposure to inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α), and interferons (IFNs) can mature DCs, enhancing their ability to present antigens to naive T cells and activate them [39]. Antigen cross-presentation by DCs further leads to the activation of $CD8^+$ CTLs, making them essential in anti-tumor immune responses [40]. Hence, immunogenic DCs support the induction of effector T cell-mediated immunity [34]. Three signals—T cell receptor/major histocompatibility complex (MHC) (signal 1), co-stimulatory molecules (signal 2), and cytokines (signal 3)—are involved in DC-T cell crosstalk [41, 42]. When DCs detect changes in the homeostatic state induced by pathogens or tissue-derived inflammatory signals, they switch from rest to active state. During this process, there are critical shifts in metabolic activity. In this regard, DCs often alter their energy generation when activated by immunogenic factors. They go from breaking down lipids and utilizing oxygen (catabolic metabolism) to generating new cells and using sugar for energy (anabolic metabolism). This metabolic shift, involving increased glycolysis and decreased OXPHOS, has significant implications for the immune response [34, 43]. Glycolysis, a key component of glucose metabolism, converts glucose into pyruvate in the cytoplasm [44–46]. The switch to lactic fermentation reroutes glycolytic intermediates into the pentose phosphate pathway (PPP). Most of the generated pyruvate transforms into lactate instead of entering the tricarboxylic acid (TCA) cycle in the mitochondria, even if oxygen is available. This can lead to the accumulation of TCA intermediates, serving as immunomodulatory signals and supporting FAS and the production of reactive oxygen species (ROS) and nitric oxide (NO) [46, 47]. These are classic characteristics of aerobic glycolysis [33, 34]. This shift triggers the activation of DCs, enabling them to produce essential biosynthetic intermediates and actively participate in initiating the immune response [48]. Specifically, upon activation through toll-like receptors (TLRs), DCs enhance their glycolytic metabolism, which supports their ability to produce pro-inflammatory cytokines and express co-stimulatory molecules essential for T cell activation [49]. Additionally, glycolysis plays a crucial role in the migration of activated DCs. It stimulates CCR7 oligomerization, which activates DCs and promotes their migration. Activated DCs express co-stimulatory markers within lymph nodes, initiating T cell priming [48]. Furthermore, the metabolic state of DCs can be influenced by their microenvironment. For instance, hypoxia and specific cytokines can alter DCs' metabolic pathways, which, as a result, affects their immunogenicity [50].

### Tolerogenic phenotype

tDCs are a unique subset of DCs, possessing immunosuppressive properties and specializing in maintaining immune tolerance [51–54]. Their unique ability to induce T cell unresponsiveness promotes tolerance rather than activation of immune response [55]. The downregulation of any of the three signals in DC-T cell interaction can lead to the generation of tDCs [41, 42]. tDCs frequently present an immature or steady-state semi-mature phenotype, characterized by low levels of MHC and costimulatory molecules and altered cytokine production [56, 57]. They are further distinguished by the expression of immunomodulatory molecules such as PD-L1 and PD-L2, reduction of CD40, CD80, and CD86 molecules, increased expression of inhibitory receptors, and production of immunosuppressive molecules such as IL-10 and transforming growth factor beta (TGF-β) [58]. In addition, tDCs usually show a decrease in IL-12 and an increase in IL-10 production and enhance their suppressive effects by interacting with other immune cells [51]. Evidence has shown that induction of B cell differentiation into regulatory B cells (Bregs) by tDCs can contribute to the tolerogenic environment. In this regard, in the TME of melanoma, tumor-associated tDCs suppress the immune response by reducing antigen presentation and stimulating Treg and Th2 responses [59–61]. The interaction between tDCs and Tregs is highly significant, as Tregs can inhibit DC maturation and maintain their tolerogenic state [62]. DCs' tolerogenic function is significantly influenced by their growth environment. This complexity is exemplified by the role of apoptotic cells and specific cytokines, which induce a semi-mature phenotype in DCs, as important factors to consider [55, 63, 64]. On the other hand, the distinguishing feature of tDCs from iDCs is their distinct metabolic features in the TME. Unlike iDCs, tDCs rely on OXPHOS and fatty acid oxidation (FAO) for energy production [65]. Given that this metabolic program is associated with a low ability to stimulate T cells, it often maintains the tolerogenic state of DCs. tDCs have also been described as reducing glycolytic flux and OXPHOS dependence during the induction of unresponsiveness in T cells in an immunological homeostatic environment [50, 66]. In addition, the target of the rapamycin (mTOR) signaling pathway is critical in regulating DC metabolic states. In iDCs, activation of the mTOR pathway is associated with increased glycolysis, while its inhibition can increase mitochondrial function toward more tolerogenic phenotypes [67]. The reason is that mTOR inhibition increases the lifespan of TLR-activated DCs by inhibiting NO production. This allows cells to continue using their mitochondria to produce adenosine triphosphate (ATP), leaving them flexible to use fatty acids or glucose as nutrients to fuel core metabolism [68]. The above process suggests that modulating mTOR activity could be a potential strategy to influence DC function and immune responses [67].

## Mitochondrial metabolic alterations in melanoma

Mitochondria promote apoptosis evasion, which underpins metabolic flexibility and resistance to targeted therapies in melanoma. Treatment-resistant phenotypes are associated with several mitochondrial adaptations, such as increased OXPHOS, glutaminolysis, dynamic fusion-fission regulation, and ROS pool modulation [69]. In contrast to the theory that the Warburg effect (glycolysis in the presence of oxygen) is the most prominent metabolic aberration in cancer, emerging data indicate that tumors encompassing melanoma can flexibly employ distinct metabolic pathways by alternating between glycolysis and mitochondrial respiration based on environmental factors [70, 71]. This metabolic plasticity may provide the basis for tumor cells to resist cytotoxicity adaptively [72]. Metabolic plasticity underlies resistance to BRAF/MEK inhibitors in melanoma. Although BRAF mutant cells have elevated glycolysis in the early phase, BRAFi exposure induces a subset of resistant cells to upregulate PGC1α and activate mitochondrial OXPHOS to compensate for the loss of glycolytic ATP production [73]. PGC1α stimulates mitochondrial biogenesis and respiration, thus facilitating survival under metabolic stress [74]. Of granting a metabolic benefit for resistant cells, mitochondrial fusion, FAO, and glutaminolysis maintain ATP production, redox homeostasis, and biosynthetic precursors, allowing to counteract therapy-induced apoptosis [75]. These mitochondrial adaptive strategies maintain therapy resistance in melanoma. Mitochondria constantly change shape by fusing or fission, which affects how cancer cells respond to treatment [69]. In resistant melanoma, mitochondria fuse, along with proteins Mitofusin1/2 (MFN1/2) and OPA1, facilitating energy production [76, 77]. In resistant cells, protein MCL1 also stabilizes mitochondria, which fuse and become unresponsive to drug treatment. Therapeutic modification of metabolic elements such as MCL1 may improve tumor responses to targeted therapy [78]. Research indicates that targeting OPA1 may serve as a viable approach to impede melanoma progression, whereas only the silencing of MFN1 or MFN2 has little effect on tumor growth [79]. On the other hand, mitochondrial fission induced by DRP1 generally activates pro-apoptotic signaling pathways. DRP1 deficiency induces mitochondrial hyperfusion, altering mitochondrial morphology and function in melanoma cells harboring active MAPK mutations. This reprogramming increases oxidative metabolism, perhaps facilitating survival and proliferation in cancer cells [77]. Glutaminolysis is a crucial mitochondrial adaptation in melanoma, sustaining energy generation and biosynthesis for tumor development. In drug-resistant cells,

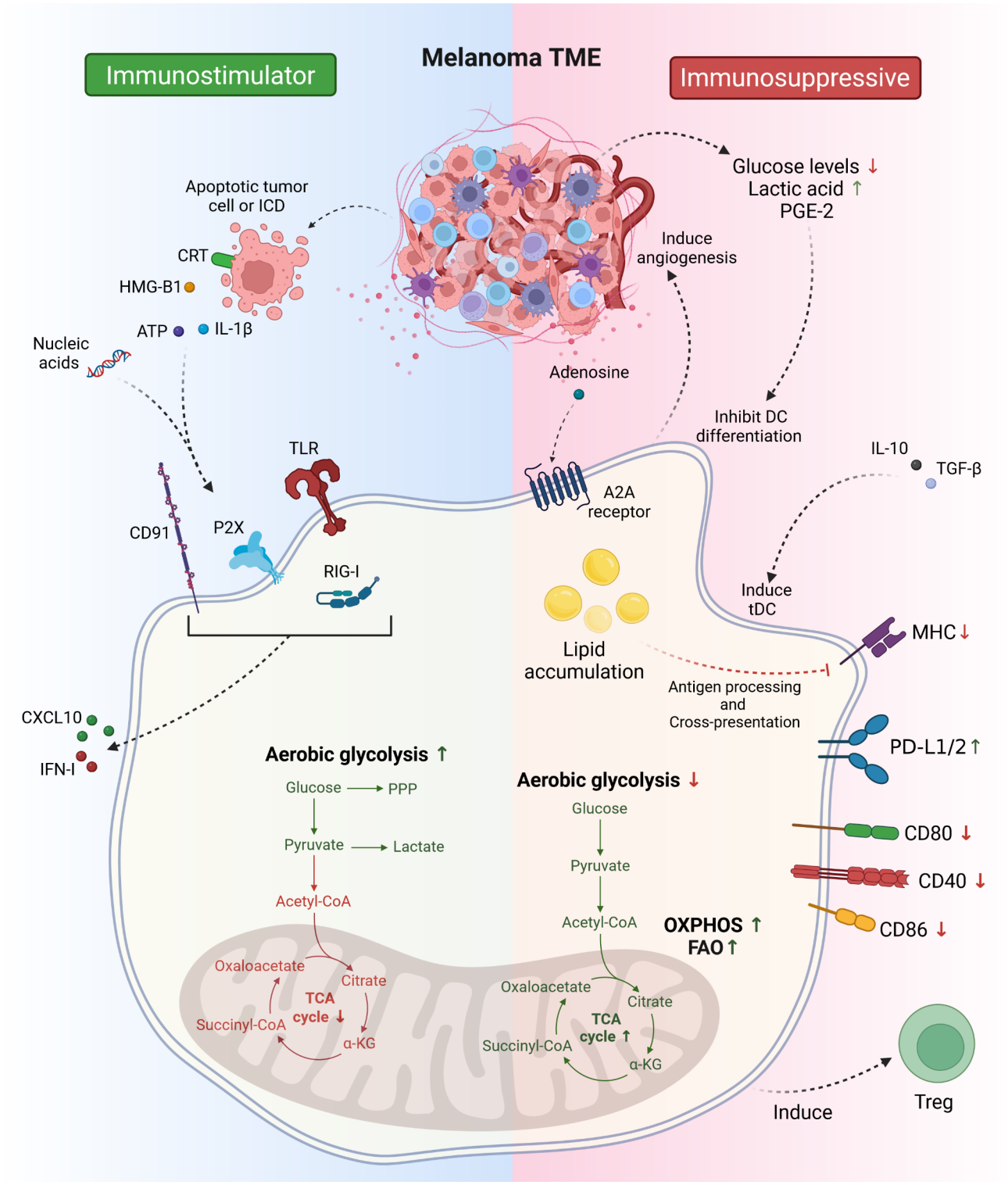


**Fig. 2** (See legend on next page.)

glutamine uptake and metabolism increase, particularly during metabolic stress [69]. The transcription factor MYC controls the process by upregulating glutaminase, which stimulates the TCA to generate ATP. Additionally, the RHOA-SRF axis promotes metabolic reprogramming and glutaminolysis in resistant melanoma [69, 80]. SOX2, a central transcription factor in melanoma, promotes tumor progression, metabolic plasticity, stemness,

(See figure on previous page.)

**Fig. 2** Melanoma TME effects on DC differentiation and metabolic pathways. Melanoma tumor cells secrete various molecules, including HMG-B1, IL-1, PGE-2, and TGF-β, which can exert both immunostimulatory and immunosuppressive effects. These molecules significantly impact the differentiation of dendritic cells and their associated metabolic pathways. For example, IL-1 promotes the development of immunogenic dendritic cells that engage in aerobic glycolysis, thereby facilitating anti-tumor responses. Conversely, TGF-β leads to the formation of tolerogenic dendritic cells that rely on OXPHOS and FAO pathways, ultimately supporting tumor growth and angiogenesiss. **Abbreviations**: DC: Dendritic cell, IL: Interleukin, IFN-I: The Type-I interferons, CD: Cluster of differentiation, MHC: Major histocompatibility complex, ATP; Adenosine triphosphate. PPP; The pentose phosphate pathway. TCA; The citric acid cycle, OXPHOS: Oxidative phosphorylation, TLR: Toll-like receptors, Treg: Regulatory T cells, PD-L1/2: program cell death 1/2, TGF-β: Transforming growth factor beta, FAO: Fatty acid oxidation, P2X: Purinergic receptors, RIG-I: Retinoic acid-inducible gene I, CXCL10: C-X-C motif chemokine ligand 10, CRT; Calreticulin, ICD: Immunogenic Cell Death, HMG-B1: High Mobility Group Box 1, PGE-2: Prostaglandin E2, TME: Tumor micro environment,

and drug resistance [81]. It is upregulated by several pathways — EGFR-STAT3, TGF-β/SOX4, and SHH/GLI signaling. It is also induced by acidic microenvironments due to lactate accumulation, leading to a metabolic switch from glycolysis to OXPHOS through inhibiting hypoxia-inducible factor 1-alpha (HIF-1α) [82]. Despite the challenges in directly targeting SOX2 as a transcription factor, targeting its regulators (e.g., EGFR inhibitors) is promising to overcome drug resistance, even though its precise function in tumor initiation is debated [69]. TRAP1, a mitochondrial HSP90 family chaperone, inhibits electron transport chain complexes II (SDH) and IV, stabilizes mitochondrial proteins, and inhibits ROS production. TRAP1 triggers mitochondrial fission and is regulated by HIF-1α, MYC, and MAPK signaling [83, 84]. TRAP1 plays a key role in resistance to MAPK inhibitors as a regulator of mitochondrial protein folding. Therefore, its suppression impairs glycolytic and respiratory metabolism, which may overcome resistance to MAPK inhibitors [69, 85]. Moreover, serum response factor (SRF), a key mediator of drug resistance, is controlled by RHOA and regulates fission-fusion balance by G-actin polymerization. RHOA-SRF signaling activates glutaminolysis by inducing glutaminase 1 with the transcription factor MYC. Inhibition of RHOA signaling greatly suppresses MYC-dependent glutamine metabolism and thus represents a candidate for overcoming melanoma drug resistance [80]. Notably, AKT1 also stimulates glycolysis through HIF-1α upregulation and OXPHOS enzymes, providing metabolic plasticity. Therefore, AKT1 compensates for bioenergetics after treatments like BRAF inhibition by enhancing glycolytic and oxidative metabolic flux, an important pathway to target melanoma plasticity [69]. These mitochondrial adaptations collectively contribute to drug resistance in melanoma by maintaining metabolic flexibility. Thus, OXPHOS modulator inhibition, fusion proteins, and metabolic reprogramming pathways have potential strategies for improving the potency of melanoma treatment.

## DCs in the TME of melanoma

DCs are considered central TME components and can promote anti-tumor T cell responses [26]. Various factors impact the functional capacity of DCs within the melanoma TME (Fig. 2). Particularly, DCs are alerted by factors originating from melanoma itself, including DAMPs released by apoptotic tumor cells. These DAMPs aid in the maturation and activation of DCs, enhancing their capability to elicit immune responses. For instance, surface calreticulin (CRT), ATP, IL-1β, high-mobility-group box 1 (HMG-B1), and nucleic acids induce alterations in DCs upon interaction with specific sensors such as RIG-I, TLR4, P2X, or CD91. DAMPs also promote the secretion of type I IFN and CXCL10, which in turn leads to the recruitment of effector immune cells to the tumor site. Consequently, inducers of immunogenic cell death (ICD), such as certain chemotherapies, hold promise for enhancing DC-mediated anti-tumor immune responses [86]. However, as evasion from immunity is a hallmark of cancer development, DC functions can be compromised in an immunosuppressive environment, resulting in an altered phenotype and increased tolerogenicity. To reveal the suppressive impact of the melanoma TME on the DCs' function, Blasio et al. developed an organotypic culture model of human cutaneous melanoma (OMC), suggesting that this culture medium is more effective for investigating TME activity mechanisms on DCs than conventional 2D co-cultures. Their model converted tumor-associated cDC2s into $CD14^+$ DCs, displaying an immunosuppressive phenotype [87]. Numerous factors within the TME suppress DC function by disrupting their differentiation, maturation, activation, and overall function [88]. In this context, prostaglandin E2 (PGE2) and gangliosides produced by melanoma cells inhibit DC differentiation and induce apoptosis [89, 90]. Additionally, TGF-β1 and IL-10 influence DC precursor differentiation towards myeloid populations with immunosuppressive characteristics [86, 91]. Furthermore, these factors suppress the expression of co-stimulatory molecules and cytokine secretion by DCs, resulting in the formation of regulatory DCs that support tumor growth by promoting angiogenesis, recruiting immunosuppressive Tregs, and suppressing T cell responses [86, 89, 91, 92]. Beyond soluble factors and regulatory molecules present in the TME, DC suppression can be triggered by irregular glycosylation patterns on the surface of tumor cells. Melanoma cells demonstrate a wide array of gangliosides and alterations in the glycosylation pattern of glycoproteins and glycolipids. Moreover, there are notable disturbances in the expression of enzymes involved in glycosylation

and deglycosylation processes, such as glycosyl-transferases and glycosidases [93, 94]. Pankaj et al. demonstrated that hyperglycosylation of prosaposin (PSAP) in tumor-associated DCs (TADCs), induced by TGF-β in the TME, hinders the lysosomal processing of apoptotic bodies. This impairment leads to reduced antigen presentation and promotes cancer immune evasion. The study further indicates that restoring normal pSAP function may enhance T cell activation and increase the effectiveness of immune checkpoint inhibitor (ICI) therapies [95]. In another study, GLYcoPROFILE characterized melanoma tumor glycol codes and DC subset function. GlcNAc, NeuAc, TF-Ag, and Fuc codons were associated with a bad prognosis; however, Man and Glc residues displayed improved survival. GlcNAc suppressed cDC2s, while Fuc and Gal decreased cDC1s and plasmacytoid DCs (pDCs), respectively. The findings imply that addressing these glycan-lectin interactions may restore DC function and offer a potential treatment for melanoma immunosuppression [96]. Furthermore, within the melanoma TME, tumor cells disrupt DC function from an immunometabolic standpoint, revealing new mechanisms of tumor-induced DC subversion. Tumor cells switch their metabolism from OXPHOS to glycolysis to fuel their rapid growth, resulting in an unfavorable microenvironment for invading DCs. This metabolic shift results in competition for scarce nutrients and the buildup of harmful metabolic byproducts in the TME, impairing immune cell function [86, 97]. It has been shown that melanoma cells in the TME diminish glucose levels, impairing glycolysis with reduced ATP production in the tumor-infiltrating DCs. Concurrently, the accumulation of lactic acid inhibits DCs' differentiation and suppresses their function [98]. The accumulation of lipids in TADCs disrupts antigen processing and cross-presentation, while fatty acids impede DC maturation. Additionally, adenosine, which increases in the melanoma TME due to ATP breakdown by CD39 and CD73 ectonucleotidases, has been shown to impair DC function through the A2A adenosine receptor [99]. Therefore, tumor cells '-related metabolic reprogramming in DCs significantly contributes to DC dysfunction and facilitates the immune evasion of melanoma tumors. However, it is possible to increase the immune system's efficiency in inducing anti-tumoral immune responses by reprogramming the tumor cells themselves. For example, Ascic et al. utilized adenoviral delivery of PU.1, IRF8, and BATF3 to reprogram tumor cells in vivo to present antigens as cDC1s. Reprogrammed tumor cells modified the TME, recruited CTLs, promoted tumor regression, and developed long-term immunity in mice melanoma models. This reprogramming occurred in human tumor spheroids and xenografts without immunosuppressive barriers [100].

## Impact of DC metabolic reprogramming on their function and tumor immune evasion in melanoma TME

As previously stated, DCs are essential mediators of anti-tumor immunity, substantially contributing to generating effective responses to checkpoint inhibitor immunotherapy. DCs' metabolic programming directly influences their transition to an immunogenic or tolerogenic state, dictating whether they can actively mitigate effective T cell responses to malignancy. However, the potential of targeting these pathways in DCs as a therapeutic strategy offers hope for effective melanoma immunotherapy [101]. Firstly, achieving this aim necessitates employing methods designed to assess metabolic processes in DCs.

Recent and advanced methods, including seahorse extracellular flux analysis, SCENITH, and metabolomics have been introduced to evaluate the metabolic profile in DCs [102]. These techniques are essential for studying cellular metabolic rewiring [103–105]. The seahorse extracellular flux analyzer, introduced in 2006, measures oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in real-time. It provides advantages over traditional techniques by presenting noninvasive measurements of key metabolic parameters [106, 107]. The effects of TLR activation on glycolysis and OXPHOS in DCs have been examined. It has also been shown that TLR activation in DCs leads to rapid glycolysis and concomitant changes in mitochondrial metabolism [108]. The single-cell energetic metabolism by profiling translation inhibition (SCENITH) technique is a recently announced method that employs flow cytometry to investigate the metabolic responses of various cell types, including DCs [104]. This technique also allows simultaneous changes in oxidative pathways, fatty acid beta-oxidation, and glutathione metabolism at different stages of human DC maturation [109]. Metabolomics studies small-molecule metabolites in cells, organs, and organisms to understand biochemical processes and metabolic pathways. It allows dynamic and in-depth immunometabolism examination and extracellular flux analysis, LC-MS, GC-MS, and SESI-HRMS, providing sensitive and real-time data. These approaches highlight DC metabolic reprogramming, crucial for immune function and targeted therapies [110]. For instance, these studies focus on the activation of DCs – induced by LPS – which induces time-dependent alterations in nucleotide pathways, the TCA cycle, and arginine metabolism [111]. In addition, single-cell RNA sequencing (scRNA-seq) reveals metabolic heterogeneity in DC populations at the single-cell level. DC populations have been shown to have different metabolic profiles, with altered glycolytic rates and oxidative metabolism determined even under similar activation conditions [109]. These approaches have demonstrated that the metabolic reprogramming of

**Table 2** Effects of metabolic pathways reprogramming on DCs function

| Metabolic Pathway | Author/ Year | Component | Impacts on DCs | References |
|---|---|---|---|---|
| **Hyperglycolysis** | Niveau et al., 2024 | C-type lectin receptor interaction with glycan patterns | Aberrant glycans delay DC TLR signaling and anti-tumor responses, promoting tumor growth. | [85] |
| | Péguet-Navarro et al., 2003 | Ganglioside involvement | Reduction in CD1a, CD54, CD80, and CD40 levels leads to DC maturation blockade, resulting in increased IL-10 and decreased IL-12 levels. | [64] |
| | Inamdar et al., 2023 | Glycolytic inhibitors | Enhance DC function, trigger high CTL responses, and support metabolite-based immunotherapy | [86] |
| **Lipid Accumulation** | Adamik et al., 2023 | Metabolic gene expression pathways, MCT1 (monocarboxylate transporter-1) | Lipid accumulation alters DC metabolism, increasing MCT1 expression and glycolysis while decreasing oxidative phosphorylation (OCR). These changes impair immunostimulatory potential and DC differentiation. | [84] |
| | Zhao et al., 2018 | Wnt5a-β-catenin-PPAR-γ signaling pathway | DCs stimulate fatty acid oxidation by modulating expression of carnitine palmitoyltransferase-1a (CPT1A), affecting immune responses. | [91] |
| | Matsushita et al., 2010 | MARCO membrane component | Upregulation in DCs pulsed with mouse tumor lysis (TP-DC) increases tumor migration; anti-MARCO antibody use reduces dendritic-like processes and alters IL-10, IL-12p70, and TNF-α production. | [93] |
| | Zewdie et al., 2024 | MerTK expression | Overexpression in DCs linked to melanoma resistance against anti-PD-1 therapy | [94] |
| | Costa silva C et al., 2024 | Intestinal microbiota interaction | Modifications in acylcarnitines, carboxylic acids, and fatty acids observed during nDC treatment. | [92] |
| **Tryptophan Deprivation** | Holtzhausen et al., 2023 | Melanoma-derived Wnt5a ligand | Upregulates the durable expression and activity of indoleamine 2,3-dioxygenase-1 (IDO) in local DCs, promoting Treg differentiation in an IDO-dependent manner. | [140] |

**Abbreviations**: DC: Dendritic Cell, TLR: Toll-Like Receptor, CTL: Cytotoxic T Lymphocyte, MCT1: Monocarboxylate Transporter-1, OCR: Oxidative Phosphorylation, Wnt5a: Wnt Family Member 5 A, PPAR-γ: Peroxisome Proliferator-Activated Receptor Gamma, CPT1A: Carnitine Palmitoyltransferase-1 A, MARCO: Macrophage Receptor with Collagenous Structure, IL: Interleukin, TNF-α: Tumor Necrosis Factor Alpha, MerTK: Mer Tyrosine Kinase, nDC: Natural Dendritic Cell, IDO: Indoleamine 2,3-Dioxygenase, Treg: Regulatory T Cell

DCs directly influences their function in the TME. For instance, DCs with the immunosuppressive phenotype exhibit elevated activity in the mTOR/AMPK pathways and dependence on fatty acid β-oxidation for metabolism [109, 112].

Secondly, identifying factors potentially driving metabolic reprogramming in melanoma-related DCs supports effectively formulating strategies to restore the appropriate function of these cells. This section will focus on common metabolic abnormalities in the TME, such as high glucose levels, lipid accumulation, tryptophan deprivation, and other factors that affect immune tolerance and cancer immune evasion (Table 2). Next, this section will address the possible ability of exosomes to cause metabolic reprogramming in melanoma-associated DCs.

## Metabolic abnormalities of DCs in the melanoma TME

### *Hyper Glycolysis*

Melanoma can be reprogrammed towards glycolysis by hyperactivating BRAF-based MAPK, inhibiting OXPHOS, and promoting glycolysis through PI3K/AKT/mTOR/ HIF-1α signaling [113, 114]. The hypoxic TME relies on the BRAF oncogene, which activates transcription factors, including MYC and HIF-1α, promoting glycolysis [115]. These transcription factors promote several critical genes related to glucose metabolism, including GLUT1, hexokinase, and lactate dehydrogenase (LDH) [116, 117]. Moreover, lactate alters CTL metabolism and immune escape function, prevents DC maturation, and increases inflammation-suppressing IL-10 in the TME, promoting melanoma invasion and metastasis [118]. Furthermore, BRAF mutations impede OXPHOS by decreasing the synthesis of MITF and PGC-1α, a critical regulator of mitochondrial activity [113]. Moreover, activating the mTOR pathway during glycolysis activates downstream transcriptional regulators, increasing the expression of inhibitory receptors like programmed cell death protein 1 (PD-1) on T cells and leading to T cell depletion and dysfunction [119]. Activated DCs primarily rely on glycolysis for energy production, membrane stability, and migration. Thus, this pathway regulates their immunological responses, encompassing cytokine synthesis, antigen presentation, T cell activation, MHC-II peptide loading, and TLR-dependent stimulating proteins [120, 121]. The 'Warburg effect,' a metabolic shift towards glycolysis, is closely associated with underdeveloped or tolerant DCs and is the main trigger of the dependence of glycolytic cancers on glucose uptake [122]. This effect significantly affects the metabolic reprogramming of DCs in the TME, affecting their immune

response capabilities. Accordingly, the higher glycolytic capacity of melanoma patients can affect mitochondrial bioenergetics in mature DCs by increasing proton leakage, decreasing ATP-related respiration, and suppressing the cross-presentation ability of DCs [123]. Several studies have investigated the effect of hyper-glycolysis on the metabolic reprogramming of DCs. Niveau and colleagues examined how C-type lectin receptors interact with specific glycan patterns in melanoma. According to the results, the binding glycan motifs, especially fucose, to cDC2s, cDC1s, and pDCs alters immunological checkpoints and cytokine/chemokine profiles. Aberrant glycans delay DC TLR signaling and anti-tumor responses and promote tumor growth [124]. Using a SCENITH approach, Niveau et al. observed altered metabolism in melanoma in DC subsets (cDC1s, cDC2s, and pDCs). Tumor cells exploit DC metabolism by reprogramming signaling through aberrant glycans and modulating pathways such as mTOR/AMPK and MCT1. These metabolic alterations negatively impact anti-tumor T cell responses [125]. Additionally, several studies provide strong evidence for gangliosides in immunosuppression. According to Navarro et al., GM3 and GD3 inhibit the proliferation of moDCs by reducing CD1a, CD54, CD80, and CD40 levels. Furthermore, DC maturation blockade induces apoptosis characterized by a significant increase of IL-10 and a corresponding decrease in IL-12 levels [89]. Moreover, glycolytic inhibitors have shown promise in enhancing DC function, triggering high CTL responses, and supporting metabolite-based immunotherapy, offering inspiration for future research and clinical applications [126].

#### *Lipid accumulation*

Melanoma cells use the acetyl-CoA-citrate pathway, FATP, and FABP to absorb fatty acids from the TME and promote lipogenesis. This metabolic mechanism helps cells develop and absorb energy. DC activation is related to improved antigen capture and presentation, enhanced cell surface markers, and secretory protein production. This mechanism is mediated by increased fatty acid synthesis, which depends on the ER and Golgi network in bone marrow-derived DCs (BMDCs) triggered by granulocyte-macrophage colony-stimulating factor (GM-CSF) [32, 127]. Although lipid production is necessary for ER and Golgi biogenesis during DC activation, lipid accumulation in DCs in malignancy is frequently linked with immune dysfunction. Lipid droplets in TADCs prevent T cell activation [128]. Lipid accumulation in DCs can compromise antigen cross-presentation and reduce antigen handling capacity by disrupting the transportation of peptide-MHC (pMHC) class I complexes to the cell surface. This suppresses the expression of CD86, increasing the production of IL-10 [129]. Cholesterol metabolism, both enzymatic and non-enzymatic, negatively affects DC function and antigen presentation, thereby reducing immune responses. Accordingly, Raccosta et al. have demonstrated that the inhibition of oxysterol receptors Liver X Receptors (LXRs) using an antagonist enhanced the differentiation of monocytes into intratumoral DCs, hindered tumor progression, and increased the efficacy of anti-PD-1 immunotherapy and adoptive T cell therapy [130]. Alternatively, the maturation of DCs is impeded by the binding and activation of the peroxisome proliferator-activated receptor (PPAR)-γ by oxidized lipids that accumulate in DCs in the TME. PPAR-γ promotes tumor progression and inhibits T cell function by increasing the synthesis and storage of fatty acids [131]. Many studies examine the correlation between lipid accumulation and metabolic reprogramming of DCs in melanoma. For instance, Adamik et al. compared 35 late-stage melanoma patients' DCs with normal donors (cancer-free controls) and found metabolic reprogramming that impairs cancer immunotherapy. The cancer patient-induced metabolic shift of the DCs abandons efficient OXPHOS for glycolysis. The switch entails increased glucose consumption, lactate overproduction, and the lactate transporter MCT1 upregulation. The metabolic aberrancies are coupled with defective lipid metabolism, defective fatty acid (FA)/phospholipid processing, and PPAR signaling pathways critical for lipid metabolism. Notably, pathways with positive clinical responses, such as FA oxidation and sphingolipid metabolism, are suppressed in the DCs. These metabolic defects hindered DC maturation and their ability to activate immune responses, reducing vaccine effectiveness. Restoring OXPHOS, normalizing glycolysis, or enhancing lipid metabolism could reverse DC dysfunction and improve therapeutic outcomes [123]. Furthermore, DCs can stimulate FAO by modulating the expression of carnitine palmitoyltransferase-1a (CPT1A), a fatty acid transporter protein, through the Wnt5a-β-catenin-PPAR-γ signaling pathway. This signaling pathway promotes Treg induction and generates immunological privilege sites, suppressing T cell activation [132]. According to the results obtained from the emerging study on the impact of intestinal microbiota, especially Faecalibacterium prausnitzii and the use of autologous natural DCs (nDCs) compared to placebo, Costa Silva et al. mentioned a better prognosis and no recurrence of melanoma in two years. Additionally, they observed modifications in acylcarnitines, carboxylic, and fatty acids during nDC treatment [133]. On the other hand, the MARCO membrane component, similar to other SR-As, exhibits the ability to bind to modified low-density lipoproteins. Recent studies have pointed to the role of MARCO in the immune response and the formation of lamellipodia-like structures and dendritic processes, which are also associated with melanoma

progression. The results showed that its upregulation in DCs pulsed with mouse tumor lysis (TP-DC) increases the tumor migration capacity. Therefore, using an anti-MARCO antibody was directly related to the disappearance of dendritic-like processes and changes in the production of IL-10, IL-12p70, and TNF-α. Moreover, using a selective inhibitor [25], its expression was shown to be related to the p38 MAPK pathway [134]. Besides, MerTK, a tyrosine kinase receptor, has also been overexpressed on DCs in melanoma-resistant anti-PD-1 therapy. In this approach, treating DCs with apoptotic melanoma cells enhanced mitochondrial respiration, FAO, and MerTK expression levels [135].

#### *Tryptophan deprivation*

The metabolism of tryptophan, an essential amino acid, can improve the intrinsic malignant features of tumor cells and impair anti-tumor immunity, making it a promising target for therapeutic development in cancer immunotherapy. The enzymes in the cytosol known as indoleamine 2,3-dioxygenase (IDO)-1, IDO-2, and tryptophan 2,3-dioxygenase (TDO-2) are responsible for the tryptophan catabolism [136]. IDO-1 in DCs can be induced by multiple factors, such as TGF-β, IL-32, and other cytokines from tumor cells, immune cells, or the DCs in the TME [137]. IDO-1, the rate-limiting enzyme in the breakdown of tryptophan, can cause immunosuppression in the TME by breaking it down and forming immunoregulatory chemicals known as kynurenines [138]. Given the role of IDO in developing tDCs in the TME, TKIs can hinder its function. In line with this, Chu et al. investigated the stimulatory effect of TKI-modified DCs on T cell activation. The findings indicated that the progression of B16 melanoma in mice was postponed by administering two TKIs, imatinib and dasatinib, due to the inhibition of tryptophan metabolism [139]. According to Holtzhausen et al., a positive correlation between the melanoma-derived Wnt5a ligand and IDO enzyme activity leads to tDCs via the catenin signaling pathway. It facilitates the melanoma-mediated immune system escape [140]. In addition, a clinical study was designed with the intervention of antigen-engineered DC vaccine to enhance the response of $CD8^+$ and $CD4^+$ polyclonal T cells against melanoma for 35 recipients. Notably, despite the significant role of a high-dose combination of IFN-α in improving outcomes, DC vaccines have a reliable place as promoters of the anti-tumor system [141].

### Exosomes as a possible inducer of metabolic reprogramming in melanoma-associated DCs

Exosomes are 30–200 nm extracellular vesicles secreted by different cell types, such as melanoma cancer cells, and contain lipid bilayer structures [142]. They are vesicles produced by the inward budding of the endosomal membrane during the growth of multivesicular bodies (MVBs). Exosomes contain cellular components, including RNA (mRNAs, miRNAs, long non-coding RNAs (lncRNAs), DNA (single-stranded, double-stranded, and mitochondrial), proteins, lipids, and metabolites, which vary depending on the origin of the exosomes [143, 144]. These vesicles can transmit these molecules to recipient tissues over extended distances, and occasionally, entire organelles, such as mitochondria, are transferred [145]. Melanoma-derived exosomes display a distinctive lipid composition that correlates with their tumorigenic potential. Exosomes in highly metastatic melanoma cells include longer saturated fatty acid chains than those derived from less metastatic cells, which contain shorter and more saturated fatty acids [146]. Palmitoylcarnitine, sphingosine 1-phosphate, elaidic carnitine, phosphatidylcholines, phosphatidylethanolamines, and glycosphingolipid ganglioside GM3 were significantly downregulated in melanoma exosomes [147]. Apart from their structural function, exosomal lipids significantly affect cargo selection since cholesterol- and sphingolipid-enriched lipid rafts serve as molecular organizers, directing the recruitment of specific proteins and macromolecules [148]. Accordingly, various molecules are present within melanoma-derived exosomes. These exosomes have been reported to carry extensive mRNA transcripts involved in metastasis, such as TOP1, ABCB5, and TYRP1. They also may transport mRNAs relevant for inflammation, including CXCL1, CXCL2 and CXCL8. The high levels of PD-L1 mRNA from plasma-derived EVs also highlight their role as predictive biomarkers since PD-L1 is a target in various ICI therapies [149, 150]. They also carry several oncogenic proteins and have become potential biomarkers even with little clinical data regarding their protein content. Several proteins like MHC-I, MART-1, MUC-18, annexins, syntenin-1, and CD44 are recognized as markers for tumor progression, angiogenesis, and metastasis [148]. Moreover, clinical studies show that exosome protein composition differs based on melanoma stages and contains migration-facilitating, apoptosis-regulating, and immune evasion proteins such as TYRP2, VLA-4, HSP70, MIA, and S100B, which are the characteristic diagnostic or prognostic markers [142]. Melanoma-derived exosomes have enhanced miRNAs, including miR-214-3p, miR-199a-3p, miR-155-5p, miR-92b-3p, and miR-183-5p, which facilitate tumor growth and metastasis [151]. MiR-106b-5p promotes epithelial-mesenchymal transition (EMT), increasing invasion and metastasis [152]. In addition, melanoma exosomes contain lncRNAs such as Gm26809, which can transform fibroblasts into cancer-associated fibroblasts (CAFs) and modify the TME [153]. Exosomal DNA represents a promising biomarker currently under investigation in melanoma. It detects BRAF mutations better than

circulating tumor DNA (ctDNA), especially during BRAF inhibitor treatment [154]. Even though mitochondrial DNA (mtDNA) has been identified in melanoma exosomes, its function remains unclear [155]. Recent studies suggest melanoma exosomes have a dual function in immunoregulation [148, 156]. They interact with DCs to present tumor antigens to T lymphocytes, leading to immune responses. MHC-I, MHC-II, and co-stimulatory molecules on exosomes enhance the activation of CTLs [157]. Nevertheless, they can also create an immunosuppressive TME and impair the functions of immune cells like DCs. These exosomes can diminish the activity of DCs, which may also obstruct antigen presentation and result in metabolic changes. For instance, these exosomes can carry pro-tolerogenic elements like MerTK-inducing ligands. When DCs were exposed to apoptotic melanoma cells in vitro, there was a notable increase in MerTK expression, heightened mitochondrial respiration, and FAO, alongside a decrease in their ability to activate T cells, all of which are characteristics associated with dysfunctional DCs [158, 159]. Non-coding RNAs represent another type of cargo that exosomes can deliver, influencing the metabolic pathways of DCs. This influence can increase mitochondrial OXPHOS, prompting DCs to manifest a tolerogenic phenotype [160]. Hence, the interaction of melanoma-derived exosomes with DCs may affect DCs, leading to metabolic modification and suppressing their anti-cancer functions.

## Conclusions and future directions

A turning point in melanoma immunotherapy is the investigation of metabolic reprogramming of DCs because there is an essential connection between metabolism and the immune system. Several factors, including lactate accumulation, lipid metabolism alterations, and tryptophan depletion, influence the metabolic alterations of melanoma-associated DCs. The factors above inhibit the maturation and antigen-presenting functions of DCs and consequently interfere with the development of DC-mediated antitumor immunity. Also, the interaction between exosomes originating from melanoma and DCs could impact DCs' functionality, causing metabolic changes that inhibit their ability to combat cancer. In this case, metabolic reprogramming of DCs is needed to get around the tumor setting, which usually changes the phenotypic status of DCs in a way that makes them less useful for activating T cells. Accordingly, focusing on these metabolic processes may enhance the performance of current immunotherapies and pave the way for new strategies to restore DC activity. Recently, it has become clear that the metabolic attributes of individual DC populations impact their immune potential and that more direct manipulations of glycolysis and OXPHOS correlate with better outcomes in melanoma patients. Furthermore, incorporating comprehensive body metabolism profiling into clinical practice may also serve as a predictor of immunotherapy response in patients. Therefore, the new arena combat for curing melanoma is not just about understanding these metabolic pathways but also about using and targeting them to develop more effective and refined treatments tailored to each patient's specific metabolic domain. A focus on these metabolic processes may enhance the performance of current immunotherapies and pave the way for new strategies that aim to restore the activity of DCs. For example, a potential future therapeutic approach is to combine ICIs with metabolic inhibitors (PGC1α inhibitors or FAO blockers) that can block tumor adaptation, making cancer cells more susceptible to immune attack and enhancing response to immunotherapy. Moreover, melanoma-derived exosomes function in immune modulation and therapeutic resistance. Exosomes not only play a role in immune evasion by carrying PD-L1, miRNAs, and immunosuppressive lipids in the TME but also carry tumor antigens, which can be used for DC-based vaccines. Exosomes engineered to carry metabolic inhibitors or immune-stimulation molecules provide a novel approach for attenuating tumor immunosuppression and promoting ICI activity. Given the immune-specific inhibitors currently used in melanoma treatment, incorporating metabolic reprogramming into current immunotherapy approaches can significantly improve clinical outcomes. Mitochondrial adaptations, metabolic plasticity, and immune metabolism may be exploited using metabolic interventions to improve antigen presentation, enhance T cell activation, and avoid immune exhaustion. In conclusion, future research should primarily look into clinical trials combining metabolic inhibitors with ICI or exosome-based therapies to develop more durable and effective treatments for melanoma.

**Acknowledgements**

Our sincere gratitude goes to authors who contributed their time and expertise to accomplish this article. Additionally, we acknowledged the Biorender website as an essential asset in designing the figures presented in our article (https://www.biorender.com).

**Author contributions**

Mina Afrashteh Nour, Mansour Rajabivahid, and Marjan Sadat Seyed Mehdi contributed to hypothesis, investigating, data gathering, and writing the main text of the manuscript. Safa Tahmasebi and Sepideh Nasirzadeh Dashtgol contributed to investigating, writing and reviewing the final draft, and designing figures and tables. Rojina Barzegar, Vahid Zarritan and Seyad Hassan Fazlazarsharabiani contributed to hypothesis and content and grammatical editing. Mahmoud Dehghani-Ghorbi, Ahmad Ghorbani Vanan, Farid Ghorbaninezhad contributed to hypothesis, scientific, structural grammatical editing, supervision, and verifying the manuscript before submission.

**Funding**

This research received no grant from any funding agency, commercial or not-for-profit sectors.

**Data availability**

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**AI utilization**
The authors declare that they have not used Artificial Intelligence in this study.

Received: 11 December 2024 / Accepted: 3 April 2025
Published online: 15 April 2025

**References**

1. Institute NC. Melanoma of the Skin-Cancer Stat Facts 2024 [Available from: https://seer.cancer.gov/statfacts/html/melan.html
2. Arnold M, Singh D, Laversanne M, Vignat J, Vaccarella S, Meheus F, et al. Global burden of cutaneous melanoma in 2020 and projections to 2040. JAMA Dermatol. 2022;158(5):495–503.
3. Hill V, Gartner JJ, Samuels Y, Goldstein AM. The genetics of melanoma: recent advances. Annu Rev Genom Hum Genet. 2013;14(1):257–79.
4. Conforti C, Zalaudek I. Epidemiology and risk factors of melanoma: A review. Dermatol Pract Concept. 2021;11(Suppl 1):e2021161S.
5. Saginala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiol Melanoma Med Sci (Basel). 2021;9(4).
6. Alexander W. The checkpoint immunotherapy revolution: what started as a trickle has become a flood, despite some daunting adverse effects; new drugs, indications, and combinations continue to emerge. P T. 2016;41(3):185–91.
7. Masoumi J, Ghorbaninezhad F, Saeedi H, Safaei S, Khaze Shahgoli V, Ghaffari Jolfayi A et al. siRNA-Mediated B7H7 knockdown in gastric cancer Lysate-Loaded dendritic cells amplifies expansion and cytokine secretion of autologous T cells. Biomedicines. 2023;11(12).
8. Cabrita R, Lauss M, Sanna A, Donia M, Skaarup Larsen M, Mitra S, et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature. 2020;577(7791):561–5.
9. Neagu M, Constantin C, Jugulete G, Cauni V, Dubrac S, Szöllősi AG, et al. Langerhans Cells—Revising their role in skin pathologies. J Personalized Med. 2022;12(12):2072.
10. Wang Y, Xiang Y, Xin VW, Wang X-W, Peng X-C, Liu X-Q, et al. Dendritic cell biology and its role in tumor immunotherapy. J Hematol Oncol. 2020;13(1):107.
11. Bronchalo-Vicente L, Río ER-D, Freire J, Calderon-Gonzalez R, Frande-Cabanes E, Gómez-Román JJ, et al. A novel therapy for melanoma developed in mice: transformation of melanoma into dendritic cells with Listeria monocytogenes. PLoS ONE. 2015;10(3):e0117923.
12. Calderon-Gonzalez R, Bronchalo-Vicente L, Freire J, Frande-Cabanes E, Alaez-Alvarez L, Gómez-Román J, et al. Exceptional antineoplastic activity of a Dendritic-Cell-Targeted vaccine loaded with A < i > Listeria peptide proposed against metastatic melanoma. Oncotarget. 2016;7(13):16855–65.
13. Boudewijns S, Bloemendal M, Haas Nd, Westdorp H, Bol KF, Schreibelt G, et al. Autologous Monocyte-Derived DC vaccination combined with cisplatin in stage III and IV melanoma patients: A prospective, randomized phase 2 trial. Cancer Immunol Immunotherapy. 2020;69(3):477–88.
14. Bol KF, Schreibelt G, Bloemendal M, van Willigen WW, Hins-de Bree S, de Goede AL, et al. Adjuvant dendritic cell therapy in stage IIIB/C melanoma: the MIND-DC randomized phase III trial. Nat Commun. 2024;15(1):1632.
15. Boudewijns S, Koornstra RHT, Westdorp H, Schreibelt G, Eertwegh AJMvd, Foppen MHG, et al. Ipilimumab administered to metastatic melanoma patients who progressed after dendritic cell vaccination. Oncoimmunology. 2016;5(8):e1201625.
16. Nirmal AJ, Maliga Z, Vallius T, Quattrochi B, Chen AA, Jacobson CA, et al. The Spatial landscape of progression and immunoediting in primary melanoma at Single-Cell resolution. Cancer Discov. 2022;12(6):1518–41.
17. Zingoni A, Antonangeli F, Sozzani S, Santoni A, Cippitelli M, Soriani A. The senescence journey in cancer immunoediting. Mol Cancer. 2024;23(1):68.
18. Tsai CH, Chuang YM, Li X, Yu YR, Tzeng SF, Teoh ST, et al. Immunoediting instructs tumor metabolic reprogramming to support immune evasion. Cell Metab. 2023;35(1):118–e337.
19. Gibney GT, Kudchadkar RR, DeConti RC, Thebeau MS, Czupryn MP, Tetteh L, et al. Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma. Clin Cancer Res. 2015;21(4):712–20.
20. Kim JM, Chen DS. Immune escape to PD-L1/PD-1 Blockade: seven steps to success (or failure). Ann Oncol. 2016;27(8):1492–504.
21. Coens C, Suciu S, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol. 2017;18(3):393–403.
22. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011;17(13):4550–7.
23. Bleve A, Durante B, Sica A, Consonni FM. Lipid metabolism and cancer immunotherapy: immunosuppressive myeloid cells at the crossroad. Int J Mol Sci. 2020;21(16):5845.
24. Wang Y, Wang D, Li Y, Zhang Y. Metabolic reprogramming in the immunosuppression of Tumor-Associated macrophages. Chin Med J. 2022;135(20):2405–16.
25. Plebanek MP, DeVito NC, Liu F, Theivanthiran B, Beasley GM, Hanks BA. 657 Characterization and therapeutic targeting of a Tumor-Associated tolerogenic DC subpopulation driven by SREBP2 and the mevalonate metabolic pathway. 2021.
26. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20(1):7–24.
27. Yin X, Chen S, Eisenbarth SC. Dendritic cell regulation of T helper cells. Annu Rev Immunol. 2021;39:759–90.
28. Del Prete A, Salvi V, Soriani A, Laffranchi M, Sozio F, Bosisio D, et al. Dendritic cell subsets in cancer immunity and tumor antigen sensing. Cell Mol Immunol. 2023;20(5):432–47.
29. He M, Roussak K, Ma F, Borcherding N, Garin V, White M, et al. CD5 expression by dendritic cells directs T cell immunity and sustains immunotherapy responses. Science. 2023;379(6633):eabg2752.
30. Castenmiller C, Keumatio-Doungtsop BC, van Ree R, de Jong EC, van Kooyk Y. Tolerogenic immunotherapy: targeting DC surface receptors to induce Antigen-Specific tolerance. Front Immunol. 2021;12:643240.
31. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016;16(9):553–65.
32. Du X, Chapman NM, Chi H. Emerging roles of cellular metabolism in regulating dendritic cell subsets and function. Front Cell Dev Biol. 2018;6:152.
33. Wculek SK, Khouili SC, Priego E, Heras-Murillo I, Sancho D. Metabolic control of dendritic cell functions: digesting information. Front Immunol. 2019;10:775.
34. O'Neill LA, Pearce EJ. Immunometabolism governs dendritic cell and macrophage function. J Exp Med. 2016;213(1):15–23.
35. Manz MG, Traver D, Miyamoto T, Weissman IL, Akashi K. Dendritic cell potentials of early lymphoid and myeloid progenitors. Blood. J Am Soc Hematol. 2001;97(11):3333–41.
36. Shortman K, Naik SH. Steady-state and inflammatory dendritic-cell development. Nat Rev Immunol. 2007;7(1):19–30.
37. Durai V. Dendritic Cell Development and Function. 2020.
38. Dalod M, Chelbi R, Malissen B, Lawrence T. Dendritic cell maturation: functional specialization through signaling specificity and transcriptional programming. Embo J. 2014;33(10):1104–16.
39. Lynch K, Treacy O, Gerlach JQ, Annuk H, Lohan P, Cabral J et al. Regulating immunogenicity and tolerogenicity of bone Marrow-Derived dendritic cells through modulation of cell surface glycosylation by dexamethasone treatment. Front Immunol. 2017;8.
40. Zimmermannova O, Ferreira AG, Ascic E, Santiago MV, Kurochkin I, Hansen MB et al. Restoring tumor immunogenicity with dendritic cell reprogramming. Sci Immunol. 2023;8(85).
41. Jacobs B, Wuttke M, Papewalis C, Seissler J, Schott M. Dendritic cell subtypes and in vitro generation of dendritic cells. Horm Metab Res. 2008;40(2):99–107.
42. Kapsenberg ML. Dendritic-cell control of pathogen-driven T-cell polarization. Nat Rev Immunol. 2003;3(12):984–93.

43. Helft J, Böttcher J, Chakravarty P, Zelenay S, Huotari J, Schraml BU, et al. GM-CSF mouse bone marrow cultures comprise a heterogeneous population of CD11c(+)MHCII(+) macrophages and dendritic cells. Immunity. 2015;42(6):1197–211.
44. Zhao X, Xing J, Li J, Hou R, Niu X, Liu R, et al. Dysregulated dermal mesenchymal stem cell proliferation and differentiation interfered by glucose metabolism in psoriasis. Int J Stem Cells. 2021;14(1):85–93.
45. Judge A, Dodd MS. Metabolism Essays Biochem. 2020;64(4):607–47.
46. Kelly B, O'Neill LA. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015;25(7):771–84.
47. Pearce EJ, Everts B. Dendritic cell metabolism. Nat Rev Immunol. 2015;15(1):18–29.
48. Krawczyk CM, Holowka T, Sun J, Blagih J, Amiel E, DeBerardinis RJ, et al. Toll-Like Receptor–induced changes in glycolytic metabolism regulate dendritic cell activation. Blood. 2010;115(23):4742–9.
49. Thwe PM, Amiel E. The role of nitric oxide in metabolic regulation of dendritic cell immune function. Cancer Lett. 2018;412:236–42.
50. Wculek SK, Khouili SC, Priego E, Heras-Murillo I, Sancho D. Metabolic control of dendritic cell functions: digesting information. Front Immunol. 2019;10.
51. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol. 2003;21:685–711.
52. Domogalla MP, Rostan PV, Raker V, Steinbrink K. Tolerance through education: how tolerogenic dendritic cells shape immunity. Front Immunol. 2017;8.
53. Morante-Palacios O, Fondelli F, Ballestar E, Martínez-Cáceres EM. Tolerogenic dendritic cells in autoimmunity and inflammatory diseases. Trends Immunol. 2021;42(1):59–75.
54. Jonny, Sitepu EC, Nidom CA, Wirjopranoto S, Sudiana IK, Ansori ANM, et al. Ex Vivo-Generated tolerogenic dendritic cells: hope for a definitive therapy of autoimmune diseases. Curr Issues Mol Biol. 2024;46(5):4035–48.
55. Zhuang Q, Cai H, Cao Q, Li Z, Liu S, Ming Y. Tolerogenic dendritic cells: the Pearl of immunotherapy in organ transplantation. Front Immunol. 2020;11:552988.
56. Kang C, Li X, Liu P, Liu Y, Niu Y, Zeng X et al. Tolerogenic dendritic cells and TLR4/IRAK4/NF-κB signaling pathway in allergic rhinitis. Front Immunol. 2023;14.
57. Sim WJ, Ahl PJ, Connolly JE. Metabolism is central to tolerogenic dendritic cell function. Mediators Inflamm. 2016;2016:2636701.
58. Wu J, Horuzsko A. Expression and function of immunoglobulin-like transcripts on tolerogenic dendritic cells. Hum Immunol. 2009;70(5):353–6.
59. Kvedaraite E, Ginhoux F. Human dendritic cells in cancer. Sci Immunol. 2022;7(70):eabm9409.
60. Heger L, Hofer TP, Bigley V, de Vries IJM, Dalod M, Dudziak D, et al. Subsets of CD1c(+) DCs: dendritic cell versus monocyte lineage. Front Immunol. 2020;11:559166.
61. Hubert M, Gobbini E, Bendriss-Vermare N, Caux C, Valladeau-Guilemond J. Human Tumor-Infiltrating dendritic cells: from in situ visualization to High-Dimensional analyses. Cancers (Basel). 2019;11(8).
62. Amodio G, Gregori S. Dendritic cells a Double-Edge sword in autoimmune responses. Front Immunol. 2012;3.
63. Hasegawa H, Matsumoto T. Mechanisms of tolerance induction by dendritic cells in vivo. Front Immunol. 2018;9.
64. Iberg CA, Hawiger D. Natural and induced tolerogenic dendritic cells. J Immunol. 2020;204(4):733–44.
65. Malinarich F, Duan K, Hamid RA, Au B, Lin WX, Poidinger M, et al. High mitochondrial respiration and glycolytic capacity represent a metabolic phenotype of human tolerogenic dendritic cells. J Immunol. 2015;194(11):5174–86.
66. Møller SH, Wang L, Ho PC. Metabolic programming in dendritic cells tailors immune responses and homeostasis. Cell Mol Immunol. 2021;19(3):370–83.
67. Amiel E, Everts B, Fritz D, Beauchamp S, Ge B, Pearce EL, et al. Mechanistic target of Rapamycin Inhibition extends cellular lifespan in dendritic cells by preserving mitochondrial function. J Immunol. 2014;193(6):2821–30.
68. Sengupta S, Peterson TR, Sabatini DM. Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. Mol Cell. 2010;40(2):310–22.
69. Huang C, Radi RH, Arbiser JL. Mitochondrial Metabolism Melanoma Cells. 2021;10(11).
70. Kim J, DeBerardinis RJ. Mechanisms and implications of metabolic heterogeneity in cancer. Cell Metab. 2019;30(3):434–46.
71. Zhang X, Tai Z, Miao F, Huang H, Zhu Q, Bao L, et al. Metabolism heterogeneity in melanoma fuels deactivation of immunotherapy: predict before protect. Front Oncol. 2022;12:1046102.
72. Alkaraki A, McArthur GA, Sheppard KE, Smith LK. Metabolic plasticity in melanoma progression and response to oncogene targeted therapies. Cancers (Basel). 2021;13:22.
73. Loftus AW, Zarei M, Kakish H, Hajihassani O, Hue JJ, Boutros C, et al. Therapeutic implications of the metabolic changes associated with BRAF Inhibition in melanoma. Cancer Treat Rev. 2024;129:102795.
74. Hartman ML, Czyz M. MITF in melanoma: mechanisms behind its expression and activity. Cell Mol Life Sci. 2015;72(7):1249–60.
75. Jin P, Jiang J, Zhou L, Huang Z, Nice EC, Huang C, et al. Mitochondrial adaptation in cancer drug resistance: prevalence, mechanisms, and management. J Hematol Oncol. 2022;15(1):97.
76. Dal Yontem F, Kim SH, Ding Z, Grimm E, Ekmekcioglu S, Akcakaya H. Mitochondrial dynamic alterations regulate melanoma cell progression. J Cell Biochem. 2019;120(2):2098–108.
77. Du F, Yang L-h, Liu J, Wang J, Fan L, Duangmano S, et al. The role of mitochondria in the resistance of melanoma to PD-1 inhibitors. J Translational Med. 2023;21(1):345.
78. Peng Z, Gillissen B, Richter A, Sinnberg T, Schlaak MS, Eberle J. Effective targeting of melanoma cells by combination of Mcl-1 and Bcl-2/Bcl-x(L)/Bcl-w inhibitors. Int J Mol Sci. 2024;25(6).
79. Boulton DP, Caino MC. Mitochondrial fission and fusion in tumor progression to metastasis. Front Cell Dev Biol. 2022;10:849962.
80. Haikala HM, Marques E, Turunen M, Klefström J. Myc requires RhoA/SRF to reprogram glutamine metabolism. Small GTPases. 2018;9(3):274–82.
81. Mirzaei S, Paskeh MDA, Entezari M, Mirmazloomi Sr, Hassanpoor A, Aboutalebi M, et al. SOX2 function in cancers: association with growth, invasion, stemness and therapy response. Biomed Pharmacother. 2022;156:113860.
82. Andreucci E, Peppicelli S, Ruzzolini J, Bianchini F, Biagioni A, Papucci L, et al. The acidic tumor microenvironment drives a stem-like phenotype in melanoma cells. J Mol Med (Berl). 2020;98(10):1431–46.
83. Joshi A, Ito T, Picard D, Neckers L. The mitochondrial HSP90 paralog TRAP1: structural dynamics, interactome, role in metabolic regulation, and inhibitors. Biomolecules. 2022;12(7).
84. Masgras I, Laquatra C, Cannino G, Serapian SA, Colombo G, Rasola A. The molecular chaperone TRAP1 in cancer: from the basics of biology to Pharmacological targeting. Semin Cancer Biol. 2021;76:45–53.
85. Zhang G, Frederick DT, Wu L, Wei Z, Krepler C, Srinivasan S, et al. Targeting mitochondrial biogenesis to overcome drug resistance to MAPK inhibitors. J Clin Invest. 2016;126(5):1834–56.
86. Hargadon KM. Strategies to improve the efficacy of dendritic Cell-Based immunotherapy for melanoma. Front Immunol. 2017;8:1594.
87. Di Blasio S, van Wigcheren GF, Becker A, van Duffelen A, Gorris M, Verrijp K, et al. The tumour microenvironment shapes dendritic cell plasticity in a human organotypic melanoma culture. Nat Commun. 2020;11(1):2749.
88. Hargadon KM. Tumor-altered dendritic cell function: implications for anti-tumor immunity. Front Immunol. 2013;4:192.
89. Péguet-Navarro J, Sportouch M, Popa I, Berthier O, Schmitt D, Portoukalian J. Gangliosides from human melanoma tumors impair dendritic cell differentiation from monocytes and induce their apoptosis. J Immunol. 2003;170(7):3488–94.
90. Sosa Cuevas E, Saas P, Aspord C. Dendritic cell subsets in melanoma: pathophysiology, clinical prognosis and therapeutic exploitation. Cancers (Basel). 2023;15(8).
91. van de Lindenberg JJ, Lougheed SM, Zomer A, Santegoets SJ, Griffioen AW, et al. Functional characterization of a STAT3-dependent dendritic cell-derived CD14(+) cell population arising upon IL-10-driven maturation. Oncoimmunology. 2013;2(4):e23837.
92. Mao Y, Poschke I, Wennerberg E, Pico de Coaña Y, Egyhazi Brage S, Schultz I, et al. Melanoma-educated CD14 + cells acquire a myeloid-derived suppressor cell phenotype through COX-2-dependent mechanisms. Cancer Res. 2013;73(13):3877–87.
93. Agrawal P, Fontanals-Cirera B, Sokolova E, Jacob S, Vaiana CA, Argibay D, et al. A systems biology approach identifies FUT8 as a driver of melanoma metastasis. Cancer Cell. 2017;31(6):804–e197.
94. De Vellis C, Pietrobono S, Stecca B. The role of glycosylation in melanoma progression. Cells. 2021;10(8).
95. Sharma P, Zhang X, Ly K, Kim JH, Wan Q, Kim J, et al. Hyperglycosylation of prosaposin in tumor dendritic cells drives immune escape. Science. 2024;383(6679):190–200.

96. Sosa Cuevas E, Roubinet B, Mouret S, Thépaut M, de Fraipont F, Charles J et al. The melanoma tumor glyco-code impacts human dendritic cells' functionality and dictates clinical outcomes. Front Immunol. 2023;14.
97. Dong H, Bullock TN. Metabolic influences that regulate dendritic cell function in tumors. Front Immunol. 2014;5:24.
98. Monti M, Vescovi R, Consoli F, Farina D, Moratto D, Berruti A et al. Plasmacytoid dendritic cell impairment in metastatic melanoma by lactic acidosis. Cancers (Basel). 2020;12(8).
99. Cekic C, Day YJ, Sag D, Linden J. Myeloid expression of adenosine A2A receptor suppresses T and NK cell responses in the solid tumor microenvironment. Cancer Res. 2014;74(24):7250–9.
100. Ascic E, Åkerström F, Sreekumar Nair M, Rosa A, Kurochkin I, Zimmermannova O, et al. In vivo dendritic cell reprogramming for cancer immunotherapy. Science. 2024;386(6719):eadn9083.
101. Plebanek MP, Sturdivant M, DeVito NC, Hanks BA. Role of dendritic cell metabolic reprogramming in tumor immune evasion. Int Immunol. 2020;32(7):485–91.
102. Zhao Q, Zhang T, Yang H. ScRNA-seq identified the metabolic reprogramming of human colonic immune cells in different locations and disease States. Biochem Biophys Res Commun. 2022;604:96–103.
103. Xiao Y, Li Y, Zhao H. Spatiotemporal metabolomic approaches to the cancer-immunity panorama: a methodological perspective. Mol Cancer. 2024;23(1):202.
104. Argüello RJ, Combes AJ, Char R, Gigan JP, Baaziz AI, Bousiquot E, et al. SCENITH: A flow Cytometry-Based method to functionally profile energy metabolism with Single-Cell resolution. Cell Metab. 2020;32(6):1063–e757.
105. Gotoh K, Takata Y, Nakashima Y, Mizuguchi S, Komori K, Kang D. Metabolic analysis of mouse bone-marrow-derived dendritic cells using an extracellular flux analyzer. STAR Protoc. 2021;2(2):100401.
106. Gu X, Ma Y, Liu Y, Wan Q. Measurement of mitochondrial respiration in adherent cells by seahorse XF96 cell Mito stress test. STAR Protoc. 2021;2(1):100245.
107. Caines JK, Barnes DA, Berry MD. The use of seahorse XF assays to interrogate Real-Time energy metabolism in cancer cell lines. Methods Mol Biol. 2022;2508:225–34.
108. van der Pelgrom LR, Everts B. Analysis of TLR-Induced metabolic changes in dendritic cells using the seahorse XF(e)96 extracellular flux analyzer. Methods Mol Biol. 2016;1390:273–85.
109. Adamik J, Munson PV, Hartmann FJ, Combes AJ, Pierre P, Krummel MF, et al. Distinct metabolic States guide maturation of inflammatory and tolerogenic dendritic cells. Nat Commun. 2022;13(1):5184.
110. Arnold K, Dehio P, Lötscher J, Singh KD, García-Gómez D, Hess C, et al. Real-Time volatile metabolomics analysis of dendritic cells. Anal Chem. 2023;95(25):9415–21.
111. Michieletto J, Delvaux A, Chu-Van E, Junot C, Fenaille F, Castelli FA. Development of an untargeted metabolomics strategy to study the metabolic rewiring of dendritic cells upon lipopolysaccharide activation. Metabolites. 2023;13(3).
112. Wu L, Yan Z, Jiang Y, Chen Y, Du J, Guo L et al. Metabolic regulation of dendritic cell activation and immune function during inflammation. Front Immunol. 2023;14.
113. Haq R, Shoag J, Andreu-Perez P, Yokoyama S, Edelman H, Rowe GC, et al. Oncogenic BRAF regulates oxidative metabolism via PGC1alpha and MITF. Cancer Cell. 2013;23(3):302–15.
114. Laurenzana A, Chilla A, Luciani C, Peppicelli S, Biagioni A, Bianchini F, et al. uPA/uPAR system activation drives a glycolytic phenotype in melanoma cells. Int J Cancer. 2017;141(6):1190–200.
115. Parmenter TJ, Kleinschmidt M, Kinross KM, Bond ST, Li J, Kaadige MR, et al. Response of BRAF-mutant melanoma to BRAF Inhibition is mediated by a network of transcriptional regulators of Glycolysis. Cancer Discov. 2014;4(4):423–33.
116. Hall A, Meyle KD, Lange MK, Klima M, Sanderhoff M, Dahl C, et al. Dysfunctional oxidative phosphorylation makes malignant melanoma cells addicted to Glycolysis driven by the (V600E)BRAF oncogene. Oncotarget. 2013;4(4):584–99.
117. Tarrado-Castellarnau M, de Atauri P, Cascante M. Oncogenic regulation of tumor metabolic reprogramming. Oncotarget. 2016;7(38):62726–53.
118. Indini A, Grossi F, Mandalà M, Taverna D, Audrito V. Metabolic interplay between the immune system and melanoma cells: therapeutic implications. Biomedicines. 2021;9(6).
119. Zhang Z, Liu S, Zhang B, Qiao L, Zhang Y, Zhang Y. T cell dysfunction and exhaustion in cancer. Front Cell Dev Biol. 2020;8:17.
120. Li Y, Wan YY, Zhu B. Immune cell metabolism in tumor microenvironment. Adv Exp Med Biol. 2017;1011:163–96.
121. Patente TA, Pelgrom LR, Everts B. Dendritic cells are what they eat: how their metabolism shapes T helper cell polarization. Curr Opin Immunol. 2019;58:16–23.
122. Goodwin ML, Gladden LB, Nijsten MW, Jones KB. Lactate and cancer: revisiting the Warburg effect in an era of lactate shuttling. Front Nutr. 2014;1:27.
123. Adamik J, Munson PV, Maurer DM, Hartmann FJ, Bendall SC, Argüello RJ, et al. Immuno-metabolic dendritic cell vaccine signatures associate with overall survival in vaccinated melanoma patients. Nat Commun. 2023;14(1):7211.
124. Niveau C, Sosa Cuevas E, Roubinet B, Pezet M, Thépaut M, Mouret S, et al. Melanoma tumour-derived glycans hijack dendritic cell subsets through C-type lectin receptor binding. Immunology. 2024;171(2):286–311.
125. Niveau C, Cettour-Cave M, Mouret S, Sosa Cuevas E, Pezet M, Roubinet B, et al. MCT1 lactate transporter Blockade re-invigorates anti-tumor immunity through metabolic rewiring of dendritic cells in melanoma. Nat Commun. 2025;16(1):1083.
126. Inamdar S, Suresh AP, Mangal JL, Ng ND, Sundem A, Wu C, et al. Rescue of dendritic cells from Glycolysis Inhibition improves cancer immunotherapy in mice. Nat Commun. 2023;14(1):5333.
127. Peng X, He Y, Huang J, Tao Y, Liu S. Metabolism of dendritic cells in tumor microenvironment: for immunotherapy. Front Immunol. 2021;12:613492.
128. Brombacher EC, Everts B. Shaping of dendritic cell function by the metabolic Micro-Environment. Front Endocrinol (Lausanne). 2020;11:555.
129. Gardner JK, Mamotte CD, Patel P, Yeoh TL, Jackaman C, Nelson DJ. Mesothelioma tumor cells modulate dendritic cell lipid content, phenotype and function. PLoS ONE. 2015;10(4):e0123563.
130. Raccosta L, Marinozzi M, Costantini S, Maggioni D, Ferreira LM, Corna G, et al. Harnessing the reverse cholesterol transport pathway to favor differentiation of monocyte-derived apcs and antitumor responses. Cell Death Dis. 2023;14(2):129.
131. Coutant F, Agaugue S, Perrin-Cocon L, Andre P, Lotteau V. Sensing environmental lipids by dendritic cell modulates its function. J Immunol. 2004;172(1):54–60.
132. Zhao F, Xiao C, Evans KS, Theivanthiran T, DeVito N, Holtzhausen A, et al. Paracrine Wnt5a-beta-Catenin signaling triggers a metabolic program that drives dendritic cell tolerization. Immunity. 2018;48(1):147–60. e7.
133. Alves Costa Silva C, Piccinno G, Suissa D, Bourgin M, Schreibelt G, Durand S, et al. Influence of microbiota-associated metabolic reprogramming on clinical outcome in patients with melanoma from the randomized adjuvant dendritic cell-based MIND-DC trial. Nat Commun. 2024;15(1):1633.
134. Matsushita N, Komine H, Grolleau-Julius A, Pilon-Thomas S, Mulé JJ. Targeting MARCO can lead to enhanced dendritic cell motility and anti-melanoma activity. Cancer Immunol Immunother. 2010;59(6):875–84.
135. Zewdie EY, Edwards GM, Hunter DM, Earp HS, Holtzhausen A. MerTK induces dysfunctional dendritic cells by metabolic reprogramming. Cancer Immunol Res. 2024.
136. Peyraud F, Guegan JP, Bodet D, Cousin S, Bessede A, Italiano A. Targeting Tryptophan catabolism in cancer immunotherapy era: challenges and perspectives. Front Immunol. 2022;13:807271.
137. Pallotta MT, Orabona C, Volpi C, Vacca C, Belladonna ML, Bianchi R, et al. Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells. Nat Immunol. 2011;12(9):870–8.
138. Munn DH, Mellor AL. IDO in the tumor microenvironment: inflammation, Counter-Regulation, and tolerance. Trends Immunol. 2016;37(3):193–207.
139. Chu C-L, Lee Y-P, Pang C-Y, Lin H-R, Chen C-S, You R-I. Tyrosine kinase inhibitors modulate dendritic cell activity via confining c-Kit signaling and Tryptophan metabolism. Int Immunopharmacol. 2020;82:106357.
140. Holtzhausen A, Zhao F, Evans KS, Tsutsui M, Orabona C, Tyler DS, et al. Melanoma-Derived Wnt5a promotes local Dendritic-Cell expression of IDO and immunotolerance: opportunities for Pharmacologic enhancement of immunotherapy. Cancer Immunol Res. 2015;3(9):1082–95.
141. Butterfield LH, Vujanovic L, Santos PM, Maurer DM, Gambotto A, Lohr J, et al. Multiple antigen-engineered DC vaccines with or without IFNα to promote antitumor immunity in melanoma. J Immunother Cancer. 2019;7(1):113.
142. Benito-Martín A, Jasiulionis MG, García-Silva S. Extracellular vesicles and melanoma: new perspectives on tumor microenvironment and metastasis. Front Cell Dev Biol. 2022;10:1061982.
143. Kim WS, Choi D, Park JM, Song HY, Seo HS, Lee DE et al. Comparison of exosomes derived from Non- and Gamma-Irradiated melanoma cancer cells as a potential antigenic and Immunogenic source for dendritic Cell-Based immunotherapeutic vaccine. Vaccines (Basel). 2020;8(4).

144. Syn N, Wang L, Sethi G, Thiery JP, Goh BC. Exosome-Mediated metastasis: from Epithelial-Mesenchymal transition to escape from immunosurveillance. Trends Pharmacol Sci. 2016;37(7):606–17.
145. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, et al. Transfer of mitochondria from astrocytes to neurons after stroke. Nature. 2016;535(7613):551–5.
146. Lobasso S, Tanzarella P, Mannavola F, Tucci M, Silvestris F, Felici C, et al. A lipidomic approach to identify potential biomarkers in exosomes from melanoma cells with different metastatic potential. Front Physiol. 2021;12:748895.
147. Palacios-Ferrer JL, García-Ortega MB, Gallardo-Gómez M, García M, Díaz C, Boulaiz H, et al. Metabolomic profile of cancer stem cell-derived exosomes from patients with malignant melanoma. Mol Oncol. 2021;15(2):407–28.
148. Li J, Wang J, Chen Z. Emerging role of exosomes in cancer therapy: progress and challenges. Mol Cancer. 2025;24(1):13.
149. Soengas MS, Hernando E. TYRP1 mRNA goes fishing for MiRNAs in melanoma. Nat Cell Biol. 2017;19(11):1311–2.
150. Bardi GT, Al-Rayan N, Richie JL, Yaddanapudi K, Hood JL. Detection of Inflammation-Related melanoma small extracellular vesicle (sEV) mRNA content using primary melanocyte sEVs as a reference. Int J Mol Sci. 2019;20(5).
151. Gerloff D, Lützkendorf J, Moritz RKC, Wersig T, Mäder K, Müller LP et al. Melanoma-Derived Exosomal miR-125b-5p educates tumor associated macrophages (TAMs) by targeting lysosomal acid lipase A (LIPA). Cancers (Basel). 2020;12(2).
152. Luan W, Ding Y, Xi H, Ruan H, Lu F, Ma S, et al. Exosomal miR-106b-5p derived from melanoma cell promotes primary melanocytes epithelial-mesenchymal transition through targeting EphA4. J Exp Clin Cancer Res. 2021;40(1):107.
153. Hu T, Hu J. Melanoma-derived exosomes induce reprogramming fibroblasts into cancer-associated fibroblasts via Gm26809 delivery. Cell Cycle. 2019;18(22):3085–94.
154. Zocco D, Bernardi S, Novelli M, Astrua C, Fava P, Zarovni N, et al. Isolation of extracellular vesicles improves the detection of mutant DNA from plasma of metastatic melanoma patients. Sci Rep. 2020;10(1):15745.
155. Cheng AN, Cheng LC, Kuo CL, Lo YK, Chou HY, Chen CH et al. Mitochondrial Lon-induced MtDNA leakage contributes to PD-L1-mediated Immunoescape via STING-IFN signaling and extracellular vesicles. J Immunother Cancer. 2020;8(2).
156. Zhou Q, Yan Y, Li Y, Fu H, Lu D, Li Z, et al. Tumor-derived extracellular vesicles in melanoma immune response and immunotherapy. Biomed Pharmacother. 2022;156:113790.
157. Leary N, Walser S, He Y, Cousin N, Pereira P, Gallo A, et al. Melanoma-derived extracellular vesicles mediate lymphatic remodelling and impair tumour immunity in draining lymph nodes. J Extracell Vesicles. 2022;11(2):e12197.
158. Li Q, He G, Yu Y, Li X, Peng X, Yang L. Exosome crosstalk between cancer stem cells and tumor microenvironment: cancer progression and therapeutic strategies. Stem Cell Res Ther. 2024;15(1):449.
159. Zewdie EY, Edwards GM, Hunter DM, Earp HS, Holtzhausen A. MerTK induces dysfunctional dendritic cells by metabolic reprogramming. Cancer Immunol Res. 2024;12(9):1268–85.
160. Zhao Y, Gao C, Liu L, Wang L, Song Z. The development and function of human monocyte-derived dendritic cells regulated by metabolic reprogramming. J Leukoc Biol. 2023;114(3):212–22.

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