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The Treatment Revolution of Melanoma: What Came Before Immunotherapy?

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Abstract. Melanoma is a biologically complex malignancy characterized by rapid progression, strong metastatic potential, and notable resistance to conventional systemic therapy. The therapeutic landscape of melanoma has been significantly reshaped by continuing advances in molecular oncology and tumor immunology in the past few decades. This review examines the major biological mechanisms involved in the development and progression of melanoma. Current treatment strategies are discussed, with particular focus on immune checkpoint inhibitors (ICIs), specifically those targeting PD-1 and CTLA-4, both of which have demonstrated long-term clinical benefits in patients with advanced melanoma. Emerging checkpoint molecules, including LAG-3, TIGIT, and TIM-3, are also described as potential targets for next-generation immunotherapeutic approaches. In addition, this review discusses recent progress in targeted treatment approaches, immune-based therapeutic development, and adoptive cellular immunotherapy. Future studies will likely concentrate on refining combination therapies while developing more personalized treatment strategies that can further improve patient outcomes in melanoma management.

Keywords: Melanoma, Immunotherapy, Immune Checkpoint Inhibitors, Treatment Evolution, MAPK Pathway

1. Introduction

Among the different forms of malignant skin cancer, melanoma is recognized as one of the most aggressive diseases and originates from melanocytes [1, 2]. Compared with other epithelial tumors, melanoma demonstrates an exceptional capacity to infiltrate surrounding tissues and metastasize to distant organs through the lymphatic and circulatory systems [1]. Because of its biological characteristics, advanced melanoma has historically been associated with unfavorable clinical outcomes and high mortality rates [3, 4]. Over the last several decades, melanoma incidence has steadily risen worldwide, particularly in geographic regions exposed to elevated levels of ultraviolet (UV) radiation [1, 3, 5]. The continuous rise in melanoma incidence, together with the difficulty of controlling metastatic disease progression, has increasingly established melanoma as an important focus within modern oncology research.

Although surgery remains highly effective for early-stage localized melanoma, the benefits of traditional systemic therapies for advanced disease have historically been limited [1, 3]. Historically, systemic treatment options primarily consisted of chemotherapy, radiotherapy, and, later, targeted

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therapy [1, 3]. Chemotherapeutic agents such as dacarbazine were widely used in advanced melanoma; however, response rates remained relatively low, and many patients experienced minimal survival benefit, with only limited improvements in overall survival, OS, and progression-free survival, PFS [1, 6]. In addition, chemotherapy often caused substantial systemic toxicity [2]. While targeted therapies directed against BRAF-mutated melanoma later improved clinical response rates and temporarily prolonged disease control [3, 7]. However, the effectiveness of these treatments often declined over time because melanoma cells gradually developed resistance through pathway reactivation and additional molecular adaptations [3, 7, 8]. Therefore, achieving durable therapeutic benefit remained a major challenge in melanoma management.

As melanoma research has progressed, it has become evident that melanoma progression is closely associated not only with genetic mutations but also with immune evasion within the tumor microenvironment [2, 4]. Together, these discoveries later provided the scientific foundation for the development of immune checkpoint inhibitors, which are now considered one of the most important breakthroughs in melanoma treatment [2, 4]. Clinical studies demonstrated that immunotherapy could significantly improve OS, PFS, and durable response rates in patients with advanced melanoma [3, 6, 8, 9]. By blocking inhibitory immune checkpoint pathways such as PD-1 and CTLA-4, ICIs restore anti-tumor immune activity and enhance immune-mediated tumor recognition [2, 9]. Consequently, immunotherapy has dramatically changed the clinical management of melanoma, shifting it from what was once considered a rapidly fatal disease into a condition that can sometimes be managed over the long term. Nevertheless, immune-related adverse events and therapeutic resistance continue to limit the long-term efficacy of ICIs in a subset of patients [2, 4, 6].

Therefore, a systematic understanding of melanoma pathogenesis, treatment evolution, and current immunotherapy strategies remains essential for improving future treatment outcomes and guiding continued research and development.

2. Pathogenesis and epidemiology

The development and progression of melanoma result from the combined influence of environmental exposure, genetic abnormalities, and alterations within the tumor microenvironment (TME) [1, 2]. Among environmental risk factors, UV radiation is considered one of the primary contributors to melanoma formation [1, 2]. Chronic UV exposure can induce direct DNA damage while simultaneously generating oxidative stress within melanocytes, resulting in the accumulation of somatic mutations [1, 2]. UV-induced damage commonly affects genes involved in cell-cycle regulation, DNA repair, and apoptosis. When DNA repair mechanisms fail to correct these alterations effectively, the progressive accumulation of mutations may ultimately drive malignant transformation and melanoma initiation [1, 2]. Intermittent intense UV exposure and repeated episodes of sunburn are closely associated with an increased risk of melanoma [1]. In addition to UV radiation, other factors, including racial differences, family history of melanoma, and atypical nevi located in chronically sun-exposed or mechanically stressed regions, may also contribute to melanoma development [1, 2].

At the molecular level, genetic alterations represent a central driver of melanoma pathogenesis. Among the most frequently identified molecular abnormalities are mutations involving the MAPK (mitogen-activated protein kinase) signaling pathway, especially BRAF and NRAS mutations [1, 2, 3]. The BRAFV600E mutation leads to constitutive activation of the MAPK/ERK signaling cascade, which promotes uncontrolled cellular proliferation, survival, and tumor progression [1, 3]. Similarly, NRAS mutations contribute to persistent stimulation of multiple downstream signaling cascades, including MAPK and PI3K-AKT pathways; both pathways play an important role in promoting

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melanoma cell proliferation and metastatic progression [1, 2]. These molecular alterations are closely related to melanoma metastasis and decreased responsiveness to therapy [1, 3, 7]. In some patients, inherited mutations affecting tumor suppressor genes may further increase susceptibility to melanoma development [1, 2].

Besides genetic alterations, the TME also plays an important role in melanoma progression [2, 4]. Although melanoma is generally considered highly immunogenic, many melanoma lesions demonstrate limited effective immune infiltration and exhibit characteristics associated with an immunosuppressive or "cold" TME [2, 4]. Immune cells that infiltrate the tumor, especially cytotoxic CD8+ T lymphocytes, often become functionally exhausted within the melanoma microenvironment, leading to reduced anti-tumor immune activity [2, 4]. The melanoma TME also contains multiple immunosuppressive cellular populations, including regulatory immune cells such as Tregs, MDSCs, tumor-associated macrophages (TAMs), together with immunosuppressive cytokines signaling that collectively suppress efficient T-cell activation [2, 4]. Furthermore, melanoma cells can upregulate immune checkpoint molecules such as PD-L1, which suppress T-cell proliferation and facilitate immune evasion [2, 4, 9]. Through these interactions, melanoma establishes an immunosuppressive microenvironment that supports tumor survival, metastatic progression, and resistance to immunotherapy.

3. Current therapeutic strategies for melanoma

The therapeutic landscape of melanoma has changed substantially over the past several decades, evolving from traditional local therapies to molecular-targeted therapy and immunotherapy [1, 3]. Earlier treatment strategies mainly included surgery, chemotherapy, radiotherapy, and later targeted therapy [3]. Surgery remains the primary treatment option for localized melanoma and continues to play a central role in early-stage disease management [3]. Surgical excision can achieve favorable long-term survival outcomes when melanoma is diagnosed before distant metastasis occurs. However, once melanoma spreads to distant organs, surgery alone becomes insufficient for effective disease control. Radiotherapy has also been used in selected clinical situations, although its contribution to long-term survival improvement remains relatively limited [1].

Before the emergence of modern immunotherapy, chemotherapy served as the principal systemic treatment option for advanced melanoma [1, 3]. Agents such as dacarbazine were historically used for metastatic melanoma; however, objective response rates remained limited, and improvements in OS and PFS were modest for many patients [1, 10]. In many cases, patients either failed to respond or developed resistance after a relatively short period of treatment. Multiple biological mechanisms contributed to these limited therapeutic outcomes, including tumor heterogeneity, genetic instability, and activation of alternative survival pathways within melanoma cells [2, 4]. Moreover, chemotherapy lacked selectivity and frequently damaged healthy tissues, producing significant systemic toxicity and adversely affecting the patient's quality of life [2]. As a result, traditional chemotherapy alone was unable to provide durable disease control for most patients with melanoma.

With advances in the understanding of melanoma research, targeted therapy gradually emerged as a major therapeutic strategy in melanoma management [3, 8]. Frequent BRAF mutations within the MAPK signaling pathway were identified in a substantial proportion of melanoma patients [1, 3]. These findings contributed to the development of BRAF and MEK inhibitors, which were designed to suppress abnormal intracellular signaling activity [7, 8]. Compared with conventional chemotherapy, targeted therapy led to higher clinical response rates while also prolonging PFS among patients carrying BRAF-mutated melanoma [7, 8]. However, treatment resistance frequently emerged during subsequent therapy [1, 3]. Reactivation of MAPK signaling pathways and additional

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molecular alterations allowed melanoma cells to continue proliferating despite ongoing targeted therapy [1, 3, 7]. Despite these advances, the long-term therapeutic benefit of targeted therapy remained limited in many patients.

The identification of immune checkpoints further transformed the therapeutic landscape of melanoma [2, 4]. Studies demonstrated that melanoma cells can express immune checkpoint molecules at high levels, such as PD-L1, which suppresses T-cell-mediated immune responses and consequently weakens overall anti-tumor immune activity [2, 9]. Based on these findings, ICIs were developed to restore immune recognition of tumor cells by blocking inhibitory checkpoints [2, 9]. Unlike chemotherapy and targeted therapy, ICIs primarily function through reactivating anti-tumor immune responses rather than exerting direct cytotoxic effects on tumor cells [2]. Clinical application of PD-1 inhibitors (including nivolumab and pembrolizumab), combined with CTLA-4 blockade therapy, has significantly improved survival outcomes and durable response rates in patients with advanced melanoma [3, 6, 8]. In some patients, immunotherapy also achieved long-term disease control that had previously been difficult to obtain with conventional systemic therapies [3, 8]. Because of these clinical benefits, ICIs have become one of the central treatment strategies in modern melanoma management.

4. Immune checkpoint inhibitors in malignant melanoma

4.1. PD-1 inhibitors

Programmed cell death protein 1 (PD-1) functions as a critical inhibitory receptor primarily expressed on activated T cells and other immune cells [2]. Under normal physiological conditions, the interaction between PD-1 and its ligands, PD-L1 and PD-L2, helps maintain immune tolerance and prevents excessive immune activation. Melanoma cells can increase PD-L1 expression, thereby reducing T-cell activation while allowing tumor cells to escape immune-mediated destruction [2, 4].

PD-1 inhibitors restore anti-tumor immune responses by blocking the interaction between PD-1 and its ligands. Nivolumab and pembrolizumab are currently among the most widely used PD-1 inhibitors in melanoma treatment [3, 6, 9]. Clinical studies have shown that PD-1 blockade significantly improved overall survival (OS), progression-free survival (PFS), and response durability compared with traditional chemotherapy approaches and earlier immunotherapies [3, 4] [9]. Long-term follow-up studies further demonstrated that some patients could maintain durable clinical responses for several years after treatment initiation [8]. These findings have supported the widespread clinical use of PD-1 inhibitors in advanced melanoma treatment [3, 9].

Although PD-1 inhibitors generally demonstrate better tolerability than earlier immunotherapeutic approaches, treatment resistance remains an important limitation [2, 4]. Several mechanisms are associated with resistance to PD-1 blockades, including impaired antigen presentation, altered interferon signaling, insufficient T-cell infiltration, and an immunosuppressive state within the TME [4]. Immune-related adverse events may also occur during treatment, affecting the skin, gastrointestinal tract, liver, endocrine organs, and lungs. These toxicities arise from overactivation of the immune system and loss of self-tolerance during immune checkpoint blockade therapy [2, 6].

4.2. CTLA-4 inhibitors

CTLA-4 (Cytotoxic T-Lymphocyte-Associated Protein 4) represents a second major immune checkpoint pathway involved in regulating T-cell activation [2]. Unlike PD-1, which mainly

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functions within the TME, CTLA-4 primarily regulates the early activation stage of T cells [2].

Ipilimumab was the first immune checkpoint inhibitor approved for the treatment of advanced melanoma, marking a major milestone in cancer immunotherapy development [3, 6]. By blocking CTLA-4 signaling, ipilimumab enhances T-cell activation and promotes anti-tumor immune responses [2]. CTLA-4 inhibition therapy has improved survival outcomes for a subset of patients with metastatic melanoma [3, 4].

Despite these clinical benefits, CTLA-4 inhibitors are associated with relatively high toxicity because of their broader effects on immune regulation [2, 6]. Adverse immune-related complications, including colitis, hepatitis, dermatitis, and endocrine dysfunction, tend to occur at a higher frequency [2]. For this reason, CTLA-4 inhibitors are now more commonly used in combination with PD-1 inhibitors rather than as monotherapy in advanced melanoma treatment [3, 6].

4.3. LAG-3

Lymphocyte-activation gene 3 (LAG-3) has recently emerged as an additional inhibitory checkpoint molecule involved in the regulation of T-cell function [4]. LAG-3 is commonly expressed on activated T cells, regulatory T cells, and exhausted tumor-infiltrating lymphocytes within the TME [4]. Increased LAG-3 expression has been associated with reduced T-cell proliferation, together with lower cytokine production, ultimately weakening anti-tumor immune responses [4].

Recent studies have demonstrated that simultaneous blockade of PD-1 and LAG-3 may improve immune activity in melanoma patients with resistance to PD-1 inhibition alone [3, 4]. Relatlimab, a monoclonal antibody targeting LAG-3, has shown promising clinical activity when combined with nivolumab in advanced melanoma treatment [3]. These findings suggest that LAG-3 may represent an important target for future combination immunotherapy strategies [11].

4.4. TIGIT

T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif (TIGIT) is a newly identified immune checkpoint receptor involved in tumor immune regulation [12]. Within the TME, TIGIT is highly expressed on CD4+ T cells, CD8+ T cells, natural killer (NK) cells, regulatory T cells, and tumor-infiltrating lymphocytes [12]. Similar to PD-1 and CTLA-4, TIGIT signaling suppresses anti-tumor immune activity and contributes to T-cell exhaustion [12].

The primary ligand of TIGIT is CD155, which is frequently expressed on the surface of tumor cells and antigen-presenting cells [12]. The interaction between TIGIT and CD155 inhibits T-cell and NK-cell activation, allowing tumor cells to evade immune destruction [12]. Some studies also suggest that increased TIGIT expression may be associated with impaired NK-cell and T-cell function, contributing to reduced anti-tumor immune activity [12].

Because of these findings, TIGIT has become a promising therapeutic target in cancer immunotherapy [12, 13]. Anti-TIGIT therapies have been investigated both as monotherapies and in combination with PD-1 inhibitors [12]. Existing research suggests that, compared with monotherapy, the combined blockade of TIGIT and PD-1 is more effective in enhancing anti-tumor immune responses [12, 13]. However, some anti-TIGIT clinical trials have produced inconsistent results, suggesting that additional studies are required before the precise clinical role of TIGIT-targeted therapy can be fully determined [12].

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4.5. TIM-3

T-cell immunoglobulin and mucin domain 3 (TIM-3) has gained increasing research attention as a novel checkpoint molecule associated with immune suppression and T-cell dysfunction within the TME [12]. TIM-3 is commonly found alongside PD-1 expression on exhausted T cells within melanoma lesions, particularly in advanced or treatment-resistant disease states [12]. Increased TIM-3 expression has been associated with impaired immune activity and adaptive resistance to immune checkpoint blockade therapy [12].

Because of its role in T-cell exhaustion, TIM-3 has recently attracted attention as a potential target for future immune checkpoint-based cancer immunotherapy development [12]. Several preclinical and early clinical studies have explored combined TIM-3 and PD-1 blockades as a possible strategy for enhancing anti-tumor immune responses [12, 13].

5. Clinical significance and limitations of ICIs

The development of PD-1 and CTLA-4 inhibitors has changed melanoma from a cancer with limited systemic treatment options into a disease in which long-term control has become achievable for a subset of patients [3, 4]. Instead of targeting the tumor directly, these therapies have shifted the overall treatment strategy by emphasizing the interaction between melanoma cells and the immune system [2]. This transformation has also influenced the broader field of oncology, with melanoma becoming one of the earliest cancers to demonstrate the clinical potential of immune checkpoint blockade.

More recently, additional checkpoint targets, including LAG-3, TIGIT, and TIM-3, have further expanded the development of combination immunotherapy strategies in melanoma [3, 12]. These emerging checkpoint pathways are now being investigated as potential therapeutic targets for patients with limited responsiveness or acquired resistance to existing PD-1 blockade therapy [12, 13].

However, immune checkpoint inhibition still faces several challenges. Clinical responses vary among different patients, and resistance remains difficult to predict and overcome [4]. Increased immune activation may also lead to immune-related toxicity, making long-term patient management more complex [2, 6]. Current research has therefore focused increasingly on biomarker identification, optimization of combination therapy strategies, and improved patient stratification to guide immunotherapy selection in a more precise manner in the future [4, 12, 14].

6. Recent progress in melanoma treatment

Recent progress in melanoma treatment has been largely driven by the development of immune checkpoint inhibitors alongside emerging combination therapy strategies [3, 7, 8]. Compared with earlier chemotherapy-based approaches, modern immunotherapy has produced more durable clinical responses and improved survival outcomes in patients with melanoma [3, 6].

Targeted therapy has contributed significantly to recent advances in melanoma treatment, particularly in patients with BRAF-mutated melanoma [3, 8]. BRAF mutations contribute to the abnormal activation of the MAPK signaling pathway through persistent oncogenic signaling within melanoma cells [1, 3]. BRAF and MEK inhibitors were developed to directly target this pathway and demonstrated important anti-tumor effects in patients with BRAF-mutated melanoma [7, 8]. Clinical studies further showed that combined BRAF and MEK inhibition produced better disease control than BRAF inhibition alone [7, 8]. However, resistance to targeted therapy frequently

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develops during treatment because of pathway reactivation and additional molecular alterations within melanoma cells [1, 3].

Alongside advances in targeted therapy, combination immunotherapy has also become another important direction in contemporary melanoma research. Combined PD-1 and CTLA-4 blockade demonstrated greater anti-tumor activity and improved response rates compared with monotherapy approaches [3, 8]. However, combination therapy is also associated with increased immune-related adverse events (irAE) toxicity, requiring careful clinical monitoring throughout treatment [6].

Recent studies have also explored combining targeted therapy with immune checkpoint blockade [7, 8]. Preclinical and clinical evidence suggest that targeted therapy may temporarily alter the TME and enhance immune-cell infiltration, potentially improving responsiveness to immunotherapy [7, 8]. However, treatment-related toxicity and optimal therapeutic sequencing remain important clinical considerations [7, 8].

Neoadjuvant immune checkpoint inhibitor therapy has also emerged as an important research area [10]. Studies have shown promising clinical activity in patients with high-risk or locally advanced melanoma, particularly when treatment was administered before surgery [10].

7. Future perspectives

Despite major advances in melanoma therapy, achieving sustained disease control remains difficult for some patients because of drug resistance and immune-related toxicity [2, 4]. As a result, current research is increasingly focused on developing more precise treatment approaches.

Adoptive cell therapy (ACT) has become one of the most actively studied areas in melanoma immunotherapy research [15, 16]. Among current ACT strategies, tumor-infiltrating lymphocyte (TIL) therapy has demonstrated promising clinical activity in melanoma [15]. Lifileucel, a TIL-based therapy, produced durable clinical responses in some patients with advanced melanoma who previously progressed after immune checkpoint blockade therapy [15].

Beyond TIL-based approaches, additional cellular approaches, including CAR-T, TCR-T, and CAR-NK therapies, are also being explored as potential strategies for improving tumor-specific immune responses [16].

Biomarker research has become increasingly important in melanoma treatment development [14]. Current studies are investigating molecular, genomic, and immune-related characteristics associated with immunotherapy responsiveness and resistance [14]. More accurate biomarker identification may enhance patient selection processes and better support more individualized treatment strategies in future clinical practice [14].

Taken together, future melanoma research is increasingly moving toward highly individualized and more precise therapeutic strategies. Continued progress will likely depend on the ability to more accurately predict treatment efficacy, minimize treatment-related toxicity, and achieve longer-lasting immune control in advanced melanoma [4, 14, 16].

8. Conclusion

Melanoma remains a highly aggressive malignancy characterized by strong metastatic potential and complex interactions within the TME [1, 3]. The introduction of targeted therapy and immune checkpoint blockade has markedly transformed melanoma management and significantly improved clinical outcomes [3, 8, 9]. Nevertheless, treatment resistance and immune-related toxicity continue to limit durable therapeutic responses in some patients [2, 4]. Current research now focuses on combination treatment strategies, adoptive cellular immunotherapy, and biomarker-guided precision

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medicine to achieve more sustained long-term disease control in advanced melanoma [12, 14, 15, 16].

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