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Mechanisms of Resistance to Immunotherapy in Melanoma: Limitations and Future Therapeutic Strategies

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Abstract. Melanoma is clinically aggressive and can metastasise early, making advanced disease difficult to control. Checkpoint inhibitors that target PD-1, PD-L1 and CTLA-4 have modified the response of anti-tumour T cells by blocking inhibitory signals. However, many patients either do not respond or relapse after initial improvement; therefore, durable disease control remains difficult for many patients. This paper reviews the main biological mechanisms underlying the reduced response to immunotherapy in melanoma. Tumour-cell-intrinsic mechanisms include defective antigen presentation, loss of tumour-associated antigens, altered interferon-γ signalling and oncogenic pathways that reduce immune visibility. Resistance is also induced by the tumour microenvironment; suppressive immune cells, inhibitory cytokines, limited T-cell infiltration, exhaustion and adverse metabolic conditions weaken the anti-tumour response. At present, the treatments available for this disease include PD-1 blockade, CTLA-4 inhibition and combination checkpoint blockade; although some have demonstrated good and prolonged responses, they are subject to inconsistent efficacy, immune-related adverse events and a lack of reliable predictive biomarkers. Recently, several rational combinations of new drugs and added immune targets have been introduced to improve the precision of treatment. In short, closer cooperation between the field of resistance biology and clinical practice is required to develop longer-lasting and more tailored immune-oncology strategies for melanoma.

Keywords: Melanoma, immunotherapy resistance, immune checkpoint inhibitors, tumour microenvironment, personalised therapy

1. Introduction

Melanoma arises from melanocytes and can spread locally and spread as a distant metastasis relatively early on. Although the frequency of this has increased in recent years, the results vary by stage. Localised melanoma can be managed by surgery; otherwise, advanced melanoma is difficult to treat due to metastatic spread and a reduced response to older chemotherapy or radiotherapy, thus affecting long-term disease control [1, 2].

Immune therapy has changed the course of melanoma, and immune-checkpoint inhibitors (ICIs) are now being used. These drugs block inhibitory pathways involving programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and thus reduce the signal that normally suppresses T-cell activity [3, 4].

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Checkpoint blockade can improve the survival rate and extend the time to disease relapse in some patients with advanced melanoma [5, 6].

These improvements have not solved the problem of resistance to checkpoint blockade. According to the above clinical data, about 55% of melanoma patients show resistance to PD-1 inhibitors, and roughly one-quarter of the patients who initially respond develop acquired resistance within two years [5]. These data show that an increase in overall survival for a population has not resolved the problem of poor response to immunotherapy in many individual patients.

Alterations have occurred at the micro-level in the cancer cells and their surrounding environment causing resistance. Tumour cells may have mutations or alterations in the signalling pathway that reduce antigen presentation or interfere with immune-responsive signalling, such as interferon-γ signalling [7, 8]. Immunosuppressive immune cells and cytokine networks outside of tumour cells in the tumour microenvironment (TME) can also reduce anti-tumour effects and lower the efficacy of ICIs [9, 10].

The TME influences whether immune cells infiltrate the tumour and whether they remain functional after entry. It contains immune cells, stromal components and extracellular matrix components and soluble mediators that can interact with melanoma cells in a way that promotes immune evasion or restricts T-cell infiltration [10]. Tumour mutational burden and neoantigen availability also affect the response to ICIs, and these factors add another layer of biological heterogeneity to melanoma immunotherapy [11, 12].

For these reasons, the resistance of melanoma immunotherapy should be regarded as a multiple-pathway phenomenon rather than a failure in a single pathway. This review will examine the tumour-intrinsic and microenvironmental reasons for reduced response to ICIs, list the defects in present-day treatments, and put forward new ideas for enhancing the duration of response and selecting appropriate patients.

2. Mechanisms of resistance

2.1. Tumour-intrinsic mechanisms

Tumour-intrinsic resistance is the change in melanoma cells that reduces their recognition by and killing effect of the immune system. The above changes can interrupt several links in the cancer-immunity cycle, including antigen presentation, interferon-responsive signalling, and maintenance of tumour immunogenicity, thus reducing the effectiveness of cytotoxic T lymphocytes [13].

The first internal way by which resistance occurs is reduced antigen presentation. For checkpoint blockade to be effective, tumour peptides must be presented by major histocompatibility complex class I (MHC-I) molecules so that CD8+ T cells can recognise malignant cells. Mutations in β-2-microglobulin (B2M), a necessary component of MHC-I, can reduce cell-surface MHC-I expression and thus fail to stimulate T-cells effectively [5, 6]. Such defects have been reported in melanoma patients who relapse after an initial response to ICIs, and they are considered acquired resistance [6]. Melanoma dedifferentiation may also reduce the expression of melanocyte-lineage antigens and thus weaken immune recognition [5].

Another tumour-cell mechanism to reduce the effect of ICI is altered interferon-γ (IFN-γ) signalling. IFN-γ normally stimulates anti-tumour immunity by upregulating the antigen-presentation machinery, enhancing MHC expression, and inducing chemokines that recruit effector T cells. Loss-of-function mutations in pathway components such as Janus kinase 1 or 2 (JAK1/2) can inhibit the downstream STAT signal and suppress the transcription of interferon-stimulated genes [7]. As a result, the tumour cells are less susceptible to immune attack, have weaker antigen

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presentation, and reduce the recruitment of cytotoxic lymphocytes; thus, they remain resistant and progress in the face of checkpoint blockade [6, 7].

Melanoma can also develop during treatment in a way that reduces immune recognition. Although melanoma often has a high mutation load, only some of these mutations result in neoantigens that are efficiently recognised by T cells. Under the pressure of the immune system, highly immunogenic clones may be eliminated, but less visible subclones still exist; this is in line with immunoediting [13]. This selection will reduce the effectiveness of antitumour T-cell responses gradually.

Oncogenic signals can alter antitumour immunity. For example, PTEN loss has been associated with reduced T-cell infiltration and stronger immunosuppressive signalling, and activation of the WNT/β-catenin pathway has been linked to poor dendritic-cell recruitment and weakened T-cell priming [9, 13]. These changes will promote the survival of the tumour and reduce its visibility and susceptibility to ICIs.

Together, these tumour-intrinsic mechanisms help the melanoma cells evade immune surveillance by reducing antigen visibility, disrupting immune-responsive signalling, and lowering tumour immunogenicity. The above cell-intrinsic modifications may also modify the surrounding TME by restricting immune cell infiltration and fostering a suppressive environment; thus, they can connect tumour-cell biology to extrinsic resistance.

2.2. Tumour microenvironment

Another reason for the TME-induced resistance is also under investigation. Melanoma cells are distributed in a network containing immune cells, stromal cells, the extracellular matrix and various soluble factors, and are not free-floating malignant cells. This local ecosystem can be suppressive; otherwise, the T cells will not be able to enter the tumour, lose their killing ability, and reduce the effectiveness of ICIs [9, 10].

One major TME-related feature is an increase in suppressive immune cells. Regulatory T cells (Tregs), tumour-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) inhibit the activity of cytotoxic T lymphocytes and natural killer (NK) cells [14]. MDSCs are particularly relevant to melanoma because they can suppress the immune system via arginase activity, reactive oxygen species, and inhibitory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) [12, 14]. Higher MDSC levels have been associated with poorer responses to immunotherapy in several studies, although this association may vary according to MDSC subtype and timing of assessment [12, 14].

Soluble signals in the TME also promote immune evasion. TGF-β, IL-10 and VEGF can inhibit dendritic cell maturation, reduce antigen presentation efficiency and attract suppressive immune cells [9]. These signals can make the tumour immune-excluded or immune-inactive. Therefore, although ICIs can restore systemic T-cell function, the effector cells may not be able to enter the tumour effectively or may remain inhibited upon infiltration [9, 10].

T-cell exclusion and exhaustion are also barriers. Some melanomas show the presence of cytotoxic lymphocytes at the tumour edge or in the stroma but fail to reach malignant cells in the tumour core and are thus unable to directly kill them [9, 10]. Sustained antigen exposure and inhibitory receptor signalling can also induce an exhausted state, characteried by reduced proliferation, impaired cytokine production, and continuous expression of receptors such as PD-1, LAG-3, TIM-3, and TIGIT [10]. This checkpoint redundancy can help explain why PD-1 blockade alone is not always effective.

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The tumour microenvironment can also become metabolically hostile to immune cells. Rapid tumour growth may cause hypoxia, nutrient depletion, acidosis and accumulation of inhibitory metabolites, all of which can impair T-cell function even when checkpoint inhibitors are present.

TME-induced resistance is generally a result of various inhibitory cell types, inhibitory signals, physical barriers, and metabolic stress. These external factors frequently increase the natural resistance of the tumour and cause both immune evasion by the tumour and dysfunction in immune cells. Therefore, the optimal combination needs to activate T cells and improve their entry into and activity within melanoma tissue.

2.3. Immune evasion strategies

The above resistance mechanisms are not in isolation but are intertwined. Melanoma immune evasion is a result of several factors: loss of antigen, multiple checkpoint signals, reduced T-cell accessibility, presence of suppressive immune cells and metabolic stress.

Melanoma is thus able to avoid the immune system by a combination of tumour-intrinsic and TME-driven mechanisms that disrupt multiple links in the cancer-immunity cycle. These patterns of evasion can be considered a reason for the reduced effectiveness of blocking a single checkpoint pathway in some patients [3, 10].

The first is a lack of antigen recognition by the immune system. Mutations in B2M reduce MHC-I presentation of tumour antigens and thus limit CD8+ T-cell recognition [5, 6]. At the same time, dedifferentiation can reduce the expression of melanocyte-associated antigen and make the tumour less immunogenic and thus less visible to the adaptive immune system [5].

Another type of immune evasion is checkpoint exploitation. PD-L1 expression on tumour cells can bind to PD-1 on T cells to inhibit the activation, proliferation and effector function of T cells [3]. CTLA-4 inhibits early T-cell activation by suppressing CD28-mediated co-stimulation [3]. Even after the therapeutic inhibition of PD-1, PD-L1 or CTLA-4, other receptors such as LAG-3, TIM-3 and TIGIT can still cause T-cell dysfunction [10].

Immune evasion is also promoted by the exclusion and dysfunction of effector cells in the TME. Stromal remodelling and suppressive biochemical signals can inhibit cytotoxic lymphocytes from reaching tumour cells [9, 10]. Even if T cells are present, after extended antigen stimulation and inhibitory signals, they will still be unable to release cytokines, multiply or kill cells [10]. Together, these barriers reduce immune-mediated clearance.

Suppressive immune cells are also in the tumour and inhibit the immune system. MDSCs, Tregs and TAMs can accumulate in the TME to suppress effector immunity through cytokine secretion, metabolic inhibition and other direct effects on immune cells [14]. Together, they constitute a tumour-permissive niche through their suppressive activity.

Melanoma resistance is generally viewed as a network of problems rather than a single point of failure. These mechanisms reduce tumour recognition, impair T-cell function and promote tumour survival through several pathways. This layered resistance is difficult to overcome with single-agent checkpoint blockade, which helps explain why some patients do not respond or later relapse.

Table 1. Summary of mechanisms of immunotherapy resistance in melanoma

Category	Mechanism	Key Features	Clinical Impact
Tumour-intrinsic	Antigen presentation loss (B2M, MHC-I)	Reduced T-cell recognition	Acquired resistance, relapse

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Table 1. (continued)

Tumour-intrinsic	IFN-γ signalling defects (JAK1/2)	Impaired immune response signalling	Primary + acquired resistance
Tumour-intrinsic	Tumour dedifferentiation	Loss of melanoma antigens	Reduced immunogenicity
TME-mediated	Immunosuppressive cells (MDSCs, Tregs, TAMs)	Cytokine secretion, T-cell suppression	Poor ICI response
TME-mediated	Cytokines (TGF-β, IL-10, VEGF)	Immune inhibition, exclusion	Immune escape
TME-mediated	T-cell exclusion	Physical + signalling barriers	Reduced infiltration
Immune evasion	Checkpoint redundancy	PD-1, CTLA-4, LAG-3, TIM-3, TIGIT	Treatment resistance
Metabolic	Hypoxia, nutrient depletion	T-cell dysfunction	Reduced efficacy

3. Current therapeutic approaches and limitations

ICIs have altered the regulation of immune checkpoints that suppress the tumour immune system in advanced melanoma, such as PD-1 and CTLA-4. However, they are not all effective in treating cancer; some patients have a sustained response, but others show no improvement or have disease relapse, and treatment side effects are also problems [13, 15].

3.1. PD-1 inhibitors

Nivolumab and pembrolizumab are often used in the treatment of advanced melanoma as PD-1 inhibitors. By inhibiting the binding of PD-1 on T cells to PD-L1 on tumours and immune cells, these drugs can help to reactivate T cells and kill tumour cells [3]. In CheckMate-037, nivolumab had a higher objective response rate than investigator-selected chemotherapy in previously treated advanced melanoma (27% versus 10%), a longer median response duration (32 versus 13 months), and fewer grade 3-4 treatment-related adverse events (14% versus 34%) [16].

PD-1 blockade still faces the problem of resistance. Antigen-presentation loss, interferon-signalling defects and suppressive TMEs can all decrease the probability of response. As a result, some patients do not experience a response to PD-1 inhibition or progress in the disease after an initial period of control [13, 17].

3.2. CTLA-4 inhibitors

CTLA-4 inhibition, generally used with ipilimumab, occurs at an earlier stage of the immune response than PD-1 blockade. CTLA-4 inhibits the activation of T cells in lymphoid organs; therefore, its suppression will enhance co-stimulation, and more tumour-reactive T cells will be generated [3].

Ipilimumab was one of the first to show a survival benefit in melanoma but using it alone has had certain deficiencies. CTLA-4 blockade generally has a lower response rate and a higher frequency of immune-related adverse events compared with PD-1 inhibitors [15]. Multiple organ damage due to toxicity can occur and must be monitored.

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3.3. Combination immunotherapy

Combination checkpoint blockade was introduced to address the deficiencies of single-agent therapy. One established combination approach for advanced melanoma is nivolumab plus ipilimumab. The two drugs work at different locations in the immune response: PD-1 blockade promotes the activity of effector T cells in the TME, and CTLA-4 inhibition expands these cells during priming and proliferation in lymphoid tissues. Together, they inhibit two distinct checkpoint pathways.

Clinical data show that nivolumab + ipilimumab improves outcomes compared with ipilimumab alone and can enhance anti-tumour activity, but any such improvement over PD-1 monotherapy must be balanced against a significantly higher toxicity [8]. Serious immune-related adverse events occur more frequently with combined treatment, limiting its use and requiring close observation [8]. Dual checkpoint blockade has also not solved the resistance problem, and thus tumour-cell mutations and TME-mediated suppression can still obstruct long-term control.

3.4. Limitations of current therapeutic approaches

Several limitations in melanoma immunotherapy have not yet been resolved. One is the problem of different responses among tumours; they have various genetic characteristics, antigenicity, microenvironment (TME), etc., and it is hard to predict whether patients will respond to therapy [13].

Immune-related adverse events (irAEs) are also problematic for treatment. Although many irAEs are manageable, some may be serious or life-threatening and may require immunosuppression [3]. This problem is relatively worse in combination therapy.

A third is the lack of a single, reliable indicator of future risk. PD-L1 expression and tumour mutational burden have both been studied; however, neither can distinguish between responders and non-responders in all cases alone [11]. Therefore, treatment selection cannot yet be fully personalised at the start of therapy.

Cost and access are also barriers. ICIs are relatively expensive, so they are not available in all hospitals and clinics, potentially limiting patient access and widening disparities in care.

In short, the present immunotherapy shows good results, such as extended life, stable response in some patients, and more precise activation of anti-tumour immunity. These strengths are balanced by limitations such as resistance, immune-related toxicity, variable efficacy and high cost. The principal strengths and deficiencies of the present strategies for melanoma immunotherapy are shown in Table 2.

Table 2. Advantages and limitations of current immunotherapy in melanoma

Advantages	Limitations
Improved overall survival compared to conventional therapies	Resistance in a substantial proportion of patients
Durable responses and long-term remission in a subset of patients	Acquired resistance following initial response
Targeted activation of antitumour immune responses	Immune-related adverse events affecting multiple organ systems
Potential for long-lasting immune memory	Variable efficacy due to tumour heterogeneity

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Table 2. (continued)

Reduced reliance on non-specific cytotoxic therapies	High cost and limited accessibility in some healthcare settings

4. Latest developments and therapeutic applications

Although some immune-checkpoint inhibitors are currently being studied and used for melanoma, immune evasion mechanisms and therapy resistance have also been observed. Tumour-intrinsic alterations and TME-mediated suppression are not always fully inhibited by single-agent checkpoint inhibition. Therefore, new therapeutic developments have recently focused on rational combinations, biomarker-guided selection of treatment options, and new immune targets that may overcome specific resistance mechanisms.

4.1. Combination therapies

Combination strategies are being used to overcome the limitations of single-agent checkpoint inhibition more frequently. Melanoma resistance may involve both changes in tumour cells and immunosuppressive characteristics of the tumour microenvironment (TME); thus, blocking only one immune pathway may be insufficient. One goal is to convert 'cold' tumours, which have a lack of T-cell infiltration, into 'hot' or inflamed tumours by attracting and activating effector cells [18]. Thus, the combinations may enhance all links in the cancer-immunity cycle rather than focusing on a single checkpoint target.

Dual PD-1 and CTLA-4 blockade is still the most common combination therapy for melanoma. CTLA-4 inhibition helps to promote priming and expansion of T cells in lymphoid organs, and PD-1 blockade increases effector function within the TME [3]. Trials of nivolumab plus ipilimumab have shown better results than those for ipilimumab alone, but this improvement also has a higher risk of serious immune-related toxicities [8].

Newer combinations are now being tested against checkpoints beyond PD-1 and CTLA-4. LAG-3 (lymphocyte activation gene-3) is associated with T-cell exhaustion and immunosuppression, so it is now being studied for treatment strategies for resistant melanoma. Relatlimab is an anti-LAG-3 antibody that, when combined with nivolumab, has improved progression-free survival in advanced melanoma compared with nivolumab alone and supports other checkpoint-targeting strategies [13].

TIGIT-guided strategies are also being explored. T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) is an inhibitory receptor expressed on activated T cells and natural killer cells, and it frequently co-localises with PD-1 in exhausted immune cells. In a phase II study of high-risk operable stage III melanoma, neoadjuvant atezolizumab plus tiragolumab had a 47.1% major pathologic response rate and a grade 3 or higher treatment-related adverse event rate of 5.9%. Although the first set of results are encouraging, more research needs to be carried out to determine whether this system can be used [19].

Combination therapy may also aim to suppress the suppressive components of the TME, not just checkpoints. Approaches to reduce the inhibitory effects of MDSCs and other immunosuppressive populations at the site can promote T-cell infiltration and function [14]. Thus, checkpoint blockade may be paired with TME-targeted strategies to address both tumour-cell and microenvironmental origins of resistance.

In short, combination strategies may improve anti-tumour immunity, but they also increase the risk of toxicity. Future studies must determine which combinations should be used, and which

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patients are most likely to benefit from them.

4.2. Biomarker-based treatment selection

Biomarker-guided treatment selection is increasingly important in melanoma immunotherapy. Given that there are many different responses to ICIs, biomarkers may help identify patients who are more likely to respond, while reducing exposure to ineffective or excessively toxic treatments.

The expression of PD-L1 has been used as a marker for the response to PD-1/PD-L1 blockade. The reason is that tumours with high PD-L1 expression may be more dependent on this inhibitory pathway for immune evasion [20]. However, PD-L1 is not sufficient on its own; some PD-L1-negative melanomas are responsive to anti-PD-1 treatment, and some PD-L1-positive tumours are not [20].

Another proposed predictor of ICI response is tumour mutational burden (TMB). A larger number of mutations is likely to produce more neoantigens for T-cell recognition by the tumour. Based on a few studies, it has been shown that melanoma patients treated with ICIs have prolonged overall survival and progression-free survival if they have a high TMB [11]. TMB is also not a complete marker on its own; mutation number does not guarantee the production of immunogenic neoantigens and does not consider antigen presentation, T-cell infiltration or TME suppression.

Broadening the molecular and immune profiles may provide more detailed information. Antigen-presentation factors, IFN-γ signalling, immune-evasion mechanisms and PTEN mutations can help distinguish between these resistance types of melanomas [5]. Therefore, integrated biomarker panels are likely to be more useful than any single measurement.

Thus, biomarkers may help distinguish patient subgroups and reduce unnecessary exposure to ineffective or toxic treatments. However, the current biomarkers still need more research to be reliably used in the choice of general melanoma immunotherapy.

4.3. Emerging immunotherapies and targets

In addition to checkpoint combinations, some new immunotherapies are also designed to overcome resistance by using cell-based treatments, personalised vaccines and TME remodelling. These measures aim to address deficiencies in the standard ICI pathway, such as weak tumour-specific T-cell responses, low antigen presentation efficiency, and immunosuppressive local microenvironments.

One typical case is adoptive cell therapy. Tumour-infiltrating lymphocyte therapy expands the number of tumour-reactive immune cells outside the body and then reintroduces them to improve the anti-tumour effect [4]. This approach may be more suitable in cases where some tumour recognition already exists, but endogenous T-cell activity is weak. Practical barriers are complex production, toxicity, high cost and the requirement for specialised treatment centres.

Personalised cancer vaccines and neoantigen-based methods are also being studied. The aim is to boost immune recognition of tumour-specific, targetable neoantigens [4, 13]. By increasing the pool of tumour-directed T cells, these strategies may reduce immune escape and may work synergistically with checkpoint blockade.

Other strategies aim to increase the permissiveness of the TME to immune attack. Potential targets include suppressive immune populations, inhibitory cytokines, metabolic barriers and innate immune pathways [13, 14]. By dealing with both tumour cell and microenvironmental resistance, these therapies may be able to make cold or excluded tumours more immune-responsive [18].

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Together, these emerging strategies move melanoma treatment towards individualised, mechanism-based immunotherapy. In the future, in addition to checkpoint blockade, exhaustion, antigen unmasking and TME suppression may also need to be addressed to improve the durability of the response and expand the group of responsive patients.

5. Discussion and future prospects

Based on the evidence provided here, immunotherapy has significantly improved the treatment of melanoma, but it is also constrained by resistance mechanisms, toxicity problems and inter-patient differences. Therefore, in addition to the speed of response, the durability and safety of the current and future strategies should also be considered, as well as how well they address the biology of resistance.

5.1. Evaluation of different immunotherapy approaches

Although immunotherapy has produced meaningful benefits for many patients with advanced melanoma, responses remain variable. Because of their durable effects and more favourable safety profile, PD-1 inhibitors such as nivolumab and pembrolizumab have been used more frequently than CTLA-4 blockade. They are more relevant when the tumours already have immune activity in the TME. Nevertheless, resistance shows that PD-1 blockade alone is not effective for many patients [5, 17].

CTLA-4 inhibitors, such as ipilimumab, are still necessary because they work at an earlier stage of the immune response to expand tumour-reactive T cells. However, as single-agent therapies, PD-1 inhibitors have shown good tolerability and higher response rates in general [3, 15], and thus their role has declined. CTLA-4 blockade is therefore often employed in combination therapy for specific indications rather than as first-line monotherapy.

Nivolumab and ipilimumab are both used to target T-cell priming and effector functions more extensively. The combination can strengthen antitumour effects compared to CTLA-4 blockade alone and supports the concept of multiple checkpoint inhibition [8]. The trade-off is a greater risk of serious immune-related side effects, so enhanced tumour control must be balanced against patient safety [8].

Overall, current approaches differ in efficacy, durability and safety. PD-1 blockade offers a relatively tolerable treatment foundation, CTLA-4 blockade contributes via immune priming, and combination therapy can strengthen the antitumour response at the expense of increased toxicity [8, 15]. None of the above strategies are completely free from non-response or recurrence, as tumour-intrinsic and TME-mediated resistance may still exist [5, 17]. Therefore, we must consider factors such as the biology of the tumour and expected benefits and potential harms.

5.2. Implications of resistance mechanisms for treatment design

Resistance biology should be applied directly in the design of treatment. As shown in previous sections, the reason for immunotherapy failure is usually not a single factor. Defective antigen presentation or impaired IFN-γ signalling can occur simultaneously with TME-mediated suppression to reduce immune recognition, T-cell entry and cytotoxic activity [10, 13].

If the cause of resistance is multifaceted, an increase in checkpoint blockade will not be effective for all patients. PD-1 inhibition can restore some T-cell function, but this effect will be small if the tumour cells are not well recognised by the immune system or if the effector cells cannot enter the

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tumour. Similarly, dual checkpoint blockade may also be impaired in the TME by MDSCs, T-cell exclusion, or metabolic stress [9, 14].

Therefore, the design of the next-generation treatment should be based on a mechanism rather than only broad immune activation. Based on the initial resistance pattern, a suitable combination may be used to enhance antigen presentation, suppress the infiltration of suppressive myeloid cells, inhibit alternative checkpoints, or improve the influx of immune cells into the tumour. This matching may increase the likelihood of a sustained response and avoid unnecessary treatment escalation in patients who are unlikely to benefit.

Thus, it can be shown that biomarkers are also clinically applicable. Markers of antigen presentation, IFN-γ signalling, immune infiltration and TME composition can be used to determine which therapies are most suitable for individual patients. Therefore, resistance mechanisms can be seen as both biological reasons for the failure of treatment and practical directions for more personalised melanoma immunotherapy.

5.3. Future outlook and personalised strategies

In the future, better treatment plans will be available for different types of tumours and immune responses in various people. A uniform treatment approach is unlikely to be optimal, because tumours differ in their genetic features, immune infiltration and resistance mechanisms. Melanoma is a particular case in which the pattern of resistance may involve antigen loss, immune evasion, checkpoint redundancy or TME-driven suppression in combination [5, 13].

Individualised strategies may combine biomarkers such as PD-L1 expression, TMB, antigen-presentation status, IFN-γ pathway activity and immune-cell infiltration. Although each biomarker has shortcomings, a panel-based approach may predict the response more accurately than any single test [11, 20]. A more granular division would be needed to determine which patients are suitable for PD-1 monotherapy and which require combination checkpoint blockade or newer options such as LAG-3, TIGIT, TIL-based therapy or vaccines.

Achieving durable responses will also require attention to multiple resistance pathways simultaneously. Given that tumour-cell changes and TME-mediated suppression often occur simultaneously, future regimens may need to combine checkpoint blockade with methods to enhance antigen presentation, suppressive immune cell inhibition, increased T-cell infiltration, and disruption of metabolic barriers [10, 14]. These approaches may help make drug-resistant or immune-excluded tumours more sensitive to treatment.

Melanoma research can help immunotherapy for other cancers. Melanoma has been a typical model for checkpoint blockade, and information obtained about the resistance of melanoma can be applied to the treatment of other solid tumours. Therefore, continuous studies on the mechanisms, biomarkers and combinations of drugs will likely enhance melanoma treatment and offer new hope for personalised cancer immunotherapy.

6. Conclusion

Immunotherapy has transformed the treatment of advanced melanoma, particularly through checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4. The above therapies can extend the life of some patients and offer them a long-term improvement in their condition; they represent a major advance over older systemic treatments. However, treatment resistance remains a major problem.

Melanoma immunotherapy resistance stems from the interaction of tumour-cell-intrinsic alterations and suppressive factors in the TME. Altered antigen presentation, disrupted IFN-γ

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signalling, dedifferentiation, suppressive immune-cell populations, inhibitory cytokines, T-cell exclusion and checkpoint redundancy can all reduce anti-tumour immunity. Therefore, these mechanisms show that a single-agent checkpoint blockade may be insufficient, and thus resistance is often not resolved by targeting just one point.

Currently and in the future, several rational combinations of these methods are being explored to address the aforementioned deficiencies. Although the methods mentioned above are promising, in practice, their application depends on a trade-off between effectiveness and toxicity, and the selection criteria for patients and combinations suitable for the biology of resistance need to be established. A clearer understanding of why some melanoma patients do not respond to immunotherapy will support more effective and personalised treatment strategies.

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