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Understanding the Complexities of Melanoma Immunobiology and a Review of Immunotherapeutic Checkpoint Inhibitors

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ABSTRACT

Melanoma immunotherapy has emerged as a promising treatment approach for advanced melanoma, a lethal form of skin cancer. Despite the remarkable clinical outcomes observed with immune checkpoint inhibitors, melanoma still poses significant therapeutic challenges. In this review, we discuss the immune landscape of melanoma, including the interactions between tumor cells and immune cells in the tumor microenvironment, according to the latest research studies. We also cover the immunobiology of melanoma and the mechanisms by which melanoma can evade immunosurveillance. Additionally, the review highlights emerging immunotherapeutic strategies that can overcome these mechanisms, including combination therapies and the use of novel agents that target immune checkpoints, their efficacy, and potential adverse effects. The goal of this timely review is to provide an up-to-date understanding of the complex interplay between melanoma and the immune system, and to identify new opportunities for developing effective melanoma immunotherapies.

Keywords: Immune checkpoint inhibitors; immune checkpoints; immunotherapy; melanoma; targeted therapy; tumor microenvironment; tumor-infiltrating lymphocytes.

INTRODUCTION

Melanoma, a kind of skin cancer caused by the malignant transformation of melanocytes, has become a major public health concern due to its high incidence rate.[1] Surgery is helpful in the early stages of melanoma, while conventional chemotherapy has limited effectiveness and is linked with a poor prognosis. Aside from that, there is a great deal of interest in novel immunotherapy for melanoma treatment.

Immunological checkpoint inhibitors that block particular proteins that hinder the immune system from attacking cancer cells are potential immunotherapeutics in the case of melanoma.[2,3]

While immunotherapy has shown promising results in clinical trials,[4] there are still barriers to its widespread use. The heterogeneous response to immunotherapy is one such hurdle, underscoring the need for a deeper understanding of the processes behind immune escape.[5]

Melanoma can avoid detection by the immune system through a number of processes, including the downregulation of MHC class I (MHC-I) molecules, which are important in antigen presentation to T cells.[6] T lymphocytes may become unable to identify and destroy cancer cells. Other immune escape strategies in melanoma include the activation of alternative signaling pathways, including the MAPK/ERK pathway, as well as the development of immunosuppressive proteins such as CTLA-4 and programmed death ligand-1 (PD-L1).

By blocking specific receptors, checkpoint inhibitors can help "release the brakes" on the immune system, allowing it to attack cancer cells more efficiently. Immunotherapy medications such as ipilimumab, a CTLA-4 inhibitor, and nivolumab and pembrolizumab, both PD-1 inhibitors, have been used to treat metastatic melanoma since 2011. Despite the potential therapeutic benefits, a wide range of immune-related adverse events (irAEs) have been reported, primarily gastrointestinal, dermatological, endocrine, and hepatic.[7] In combination therapy with ipilimumab and nivolumab, IrAEs have also increased. Nonetheless, the development of checkpoint inhibitors marks a significant step in the treatment of melanoma and other cancers, but much needs to be learned about these drugs and how to best use them.

REVIEW

According to available data, the incidence and mortality rates for melanoma in 2020 were 325 000 and 57 000, respectively.[8,9] In 2023, there are expected to be 89 070 new cases of skin melanoma in situ and 97 610 new cases of invasive melanoma of the skin.[1,10]

Overall, the lifetime risk of melanoma is around 2.6% (or 1 in 38) for Caucasians, 0.1% (1 in 1,000) for Black people, and 0.6% (1 in 167) for Hispanic ancestors.[11] A wide range of variables can raise the likelihood of melanoma. UV (ultraviolet) exposure is responsible for the vast majority of instances.[12] Sunburns at any age (childhood, adolescence, and adulthood) can raise the risk of developing melanoma later in life.[13] Unlike BCC and SCC, which are significantly associated with continuous sun exposure, melanoma is substantially bound to a pattern of intermittent sun exposure.[14] Other risk variables, such as the presence of nevi and host phenotype, have been found.

Approximately 10% of patients with melanoma have a first- or second-degree relative with the disease.[15] To date, two high-risk melanoma susceptibility genes, CDKN2A and CDK4, have been found, with a third gene, p14 (ARF), suspected of also having a role.[16] All of these data indicate that melanoma is a complex, multifactorial disease.

Experiments have shown that UV radiation can cause genetic changes such as tumor-initiating DNA mutations triggered by polymorphisms in nucleotide-excision repair (NER) genes and inflammatory responses involving IFN-producing macrophages and neutrophil infiltration, which are linked to apoptosis inhibition.[17,18] Multiple molecular pathways have been identified in melanomagenesis, including the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, the protein kinase B (AKT) pathway, the cell-cycle regulation pathway, the pigmentation-related pathway, the p53 pathway, epigenetic factors, and others.[19]

Mutations are responsible for the dysfunction of the MAPK/ERK pathway.[20] In 2002, a comprehensive genome-wide screen discovered BRAF somatic mutations in 66% of malignant melanomas.[21] These mutations, particularly the V600E codon, enhance BRAF protein kinase activity and dysregulation of the MAPK/ERK pathway, resulting in sustained cell growth and proliferation.[20] Non-V600 variants of the BRAF gene have also been found in melanoma, occurring in 5-16% of clinical cases.[22] Before the advent of immunotherapy, there were no therapeutic options for non-BRAF mutant melanoma. While selective BRAF inhibitors such as vemurafenib, dabrafenib, and the MEK inhibitor trametinib have been useful in the treatment of BRAF mutant melanoma, there were no therapeutic options for non-BRAF mutant melanoma before the advent of immunotherapy.[23]

As already mentioned, inflammatory responses play a crucial role in carcinogenesis. Tumor necrosis factor (TNF), IFN-, interleukins, and other immune cells have been studied to get a better understanding of the biology and microenvironment of melanoma.[20] The immune system has long been recognized as defending the host from malignancies and decreasing tumor cell development. Burnet and Thomas both contributed to the immunosurveillance concept in the 1950s, which is one of three phases (elimination, i.e., immunosurveillance, equilibrium, and escape) of cancer immunoediting, the process of limiting tumor proliferation.[24] T-cells, which recognize tumor antigens and induce immunological destruction of growing cancer, mediate the latter.[25]

Immunogenic malignancies, especially melanoma, can avoid immune responses through a variety of mechanisms, including deviations in antigen presentation machinery, activation of negative regulatory pathways, and recruitment of immunosuppressive cell populations.[26] The tumor microenvironment (TMI), with a range of cell types known as tumor-infiltrating lymphocytes (TILs), supports these pathways.[27] TILs are a heterogeneous group of immune cells that include functionally exhausted T cells, tolerogenic or T-regulatory (Treg) cells, dendritic cells (DCs), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs), macrophages, and others.[28]

The majority of TILs are cytotoxic CD8+ T cells, which are thought to be the most effective effectors in the anti-cancer immune response.[29] Chronic exposure to the same antigen seen in cancer, on the other hand, causes significant changes in T cell activation and differentiation. This results in the formation of dysfunctional or exhausted CD8+ T cells, T lymphocytes with reduced growth and cell recognition capacity, and high concentrations of the immunological checkpoints PD-1 and CTLA-4.[29,30] as well as other co-inhibitory receptors such as T cell immunoglobulin and mucin domain 3 (TIM-3).[31] T cells that are regulatory or tolerogenic (Treg) are a kind of T cell that suppresses the immune response. They maintain homeostasis and self-tolerance in physiological settings. Activated Tregs exhibit constitutive overexpression of PD-1 and CTLA-4 receptors as well as the production of immunosuppressive substances such as IL-10 and INF-.[32,33]

The surface immunophenotype and function of the B cell types observed in the TME differ significantly. The researchers found naive B cells, memory B cells, activated memory B cells, and plasmablasts. The tumor-associated B cells (TAB) are hypothesized to be indicators of enhanced metastatic capability in melanoma.[32,34]

Natural killers (NKs) are granular lymphocytes that are involved in the recognition and eradication of virus-infected and transformed cells. NK cells in the TME, on the other hand, are often poor and concentrate around the stroma, not in direct contact with tumor cells. Furthermore, melanoma cells secrete immune suppressive molecules that induce Treg accumulation, which suppresses NK cells.[32,35]

Dendritic cells are the immune system's core cells. They deliver antigens to naive T cells and activate them to start the immunological response. DCs in TME are immature and exhibit fewer maturation markers. They also have functional abnormalities such as poor cytokine synthesis, decreased antigen presentation, and decreased migration, all of which contribute to a diminished immune response.[5,32]

Melanoma TILs are enriched for specificity for melanoma-associated antigens (MAGEs), which include cancer-testis antigens (CTAs) and neo-antigens, which carry unique self-antigen epitopes. Neo-antigens are formed from tumor somatic mutations and contribute to tumor immunogenicity,[36,37] on which immunotherapeutic therapies are based.

Immunotherapy is an innovative cancer treatment that strengthens the humoral and cellular immune systems.[2] The earliest instance of immunotherapy may be found in the last decade of the 1800s, when William B. Coley applied

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streptococcal pathogens to inject into a patient with incurable metastatic sarcoma.[38] Coley's approach was not extensively used due to the absence of a recognized mechanism and the potential risks of infection with Coley's toxins. However, the discovery of the first immune checkpoint molecule, CTLA-4, by Brunet and his team in 1987, followed by the discovery of another checkpoint molecule, PD-1, by Tasuku Honjo in 1992, and the identification of CTLA-4 functions by Jim Allison and colleagues, all contributed to the development of the new scientific field of immunology.[39] Jim Allison et al. pioneered the idea of immune checkpoint blockade (ICB) for cancer therapy based on these findings.[36]

The co-inhibitory receptors on the surface of T lymphocytes are cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1). The CTLA-4 immune checkpoint is regarded as the "leader" of the immunological checkpoints.[29] Before activation, conventional T-cells exhibit a small amount of CTLA-4 in their physiologic condition. CTLA-4 expression increases during activation and restricts T-cell activation by binding to B7 on the antigen-presenting cell and providing inhibitory signals. PD-1, like CTLA-4, decreases T-cell proliferation and diminishes T-cell activation following binding to programmed death ligand 1 (PD-L1).[40] These inhibitory receptors, known as immunological checkpoints, are critical for preventing the harmful effects of a continuing immune response to infections on healthy tissues and, as a result, for maintaining immune tolerance.[39] However, high levels of immune checkpoints, as well as their upregulation and use by cancer cells to evade immunosurveillance, can lead to cancer spread and the ineffectiveness of traditional chemotherapy and radiotherapy.

Immune checkpoint inhibitors (ICIs) are cancer immunotherapeutic medications that stimulate anti-cancer immune responses by targeting co-inhibitory receptors on T cell surfaces.[3] Anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies are the most commonly used immune checkpoint inhibitors today. Ipilimumab, the first anti-CTLA-4 antibody, was licensed by the FDA in 2011 for the treatment of advanced metastatic melanoma. Between March 2011 and August 2018, six checkpoint inhibitors targeting the PD-1/PD-L1 pathway were authorized in the United States for the treatment of 14 diseases, including Nivolumab and Pembrolizumab (PD-1 inhibitors) for metastatic melanoma.[29,41]

In early experiments, in vivo treatment with anti-CTLA-4 antibodies resulted in tumor rejection. Furthermore, this rejection resulted in immunity to secondary tumor cell exposure.[4] Long-term survival data from Ipilimumab phase II and phase III studies in unresectable or metastatic melanoma revealed a plateau in the survival curve beginning about 3 years, which was regardless of previous therapy or Ipilimumab dosage. These findings contribute to a growing body of evidence supporting the long-term survival of ipilimumab-treated individuals with advanced melanoma.[42] Despite the promising therapeutic effects, a wide range of immune-related adverse events (irAEs) have been reported, with an incidence of 60–65% in the skin (pruritus, rash), gastrointestinal tract (nausea, diarrhea), liver, and endocrine organs (thyroid disorders).[7]

Anti-PD-1 and anti-PD-L1 antibodies have been used successfully to treat metastatic melanoma. According to research, anti-PD-1 medication can provide a full response in as little as 80 days.[29] However, not all patients responded to the treatment, implying the presence of additional inhibitory pathways in T-cell dysfunction.[43] Furthermore, PD-1 and PD-L1 inhibitors have been linked to irAEs and have been linked to gastrointestinal, dermatological, endocrine, and hepatic side effects. Combination treatment with an anti-CTLA-4 antibody (Ipilimumab) and an anti-PD-1 antibody (Nivolumab) was studied due to the differences and possibly complementary effects of both types of immune checkpoint inhibitors.36 For the combination and monotherapy, the objective response rate was 58% versus 19%, and the median progression-free survival was 11.5 versus 2.9 months, respectively.[40] Combination therapy can frequently boost the effectiveness of therapy for immunologically cold cancers. Although combination therapy outperformed either agent alone in terms of long-term efficacy in metastatic melanoma, the incidence of adverse effects increased.[43]

Multiple studies and laboratory tests revealed the diversity of immune checkpoints, which may help in the development of new immunotherapeutic agents and reduce the possibility of resistance to widely used anti-CTLA-4 and anti-PD-1 antibodies. LAG-3, or lymphocyte activation gene-3, is the most promising developing ICB target.[36] LAG-3, lymphocyte activation gene 3, is a cell surface protein expressed on CD4+ and CD8+ T cells, NK cells, B cells, and plasmacytoid dendritic cells.[43] LAG-3 is a co-inhibitory receptor that works in tandem with the PD-1 receptor. Although its functions are not fully understood, it has been demonstrated that combining anti-LAG-3 and anti-PD-1 antibodies significantly improved therapeutic activity.[43] The FDA authorized this combination, known as Relatlimab, as a therapeutic option for unresectable or metastatic melanoma in March 2022.[44]

Despite great effectiveness and advances in immune checkpoint inhibition, incidences of therapy resistance persist. More research is needed to identify potential resistance causes and predict responses to immune checkpoint inhibitors. According to a thorough evaluation of large-sample meta-analyses, tumor mutational burden (TMB) can be a useful measure for predicting the potential advantages of immunotherapy in melanoma.45 Despite limitations, future research studies on the relationship between TMB and immunotherapy will help in

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understanding the shortcomings of currently available therapies and in the development of new and improved treatment approaches.

CONCLUSIONS

Melanoma immunotherapy is a fast-emerging area that has the potential to significantly improve patient outcomes. The development of immune checkpoint inhibitors has transformed the melanoma therapy landscape, although resistance to these medications remains a serious concern. In recent years, our understanding of melanoma immunobiology has improved, demonstrating the intricate processes by which melanoma cells avoid immunosurveillance. This has resulted in the discovery of new therapeutic targets, such as the tumor microenvironment and the innate immune system. However, transforming these discoveries into effective clinical therapies requires additional research and development.

Future research should focus on developing novel biomarkers that might predict immunotherapy response and guide treatment decisions. Furthermore, a better understanding of the mechanisms underlying immune checkpoint inhibitor resistance is required to develop strategies to overcome this challenge. The impact of the tumor microenvironment and immune system on the development of melanoma and response to therapy will also be important for creating novel therapeutic methods.

Despite these challenges, advances in melanoma immunotherapy represent an important step forward in the treatment of this fatal illness. We could strive to improve outcomes and provide better care for patients with melanoma as we continue to enhance our understanding of the immunobiology of the disease and create novel treatment methods.

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